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Keksinnön nimitys
Title of invention

**"Polycyclic compounds as potent alpha2-adrenoceptor antagonists"**
**(Polysykliset yhdisteet tehokkaina alfa2-adrenoseptoriantagonisteina)**

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Marketta Tehikoski
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# POLYCYCLIC COMPOUNDS AS POTENT ALPHA2-ADRENOCEPTOR ANTAGONISTS

## FIELD OF THE INVENTION

The present invention relates to pharmacologically active arylquinolizine derivatives and related compounds and to their pharmaceutically acceptable salts and esters thereof, as well as to pharmaceutical compositions containing them and to their use as alpha2 antagonists.

## BACKGROUND OF THE INVENTION

Some compounds exhibiting alpha adrenergic activity are well known in the art. It is also generally known and accepted in the art that those compounds may be used for the treatment of a wide variety of diseases and conditions of the peripheric system and the central nervous system (CNS).

The alpha adrenergic receptors can be divided on a pharmacological basis into alpha1- and alpha2-adrenoceptors, which can both be further divided into subtypes. Three genetically encoded subtypes, namely alpha2A-, alpha2B- and alpha2C-adrenoceptors, have been discovered in human. Accordingly, alpha2-adrenoceptors in humans have been subdivided into three pharmacological subtypes known as alpha2A-, alpha2B- and alpha2C-adrenoceptors. A fourth, pharmacologically defined subtype, alpha2D, is known in rodents and in some other mammals, and it corresponds to the genetically defined alpha2A-adrenoceptors.

The alpha2-adrenoceptor subtypes have distinct tissue distributions and functional roles. For instance, while alpha2A-adrenoceptors are widely expressed in various tissues, alpha2C-adrenoceptors are concentrated in the CNS, and they appear to play a role in the modulation of specific CNS-mediated behavioural and physiological responses.

Compounds that are non-specific to any of the above-mentioned alpha2 subtypes, and compounds that are specific to certain alpha2 subtypes, are already known. For example, atipamezole is a non-specific alpha2 antagonist. Atipamezole has been described in, for example, EP-A-183 492 (cf. p.13, compound XV) and Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582. U.S. Patent No. 5,902,807 describes compounds that are selective antagonists for the alpha2C subtype and may be used in the treatment of mental illness, e.g. mental disturbance induced by stress. Such compounds include, for example, MK-912 and BAM-1303. Furthermore, WO-A-99 28300 discloses substituted imidazole derivatives having agonist-like activity for alpha2B- or 2B/2C-adrenoceptors. In addition, WO 01/64645 relates to derivatives of quinoline useful as alpha2 antagonists, as well as to selective alpha2C antagonist agents. The disclosures of all documents cited above in this paragraph are incorporated by reference herein.

Several arylquinolizine derivatives and related compounds have been described in the literature, some of which possess valuable pharmaceutical effects. For example, U.S. Patents No. 4,806,545 and 4,044,012 describe 1,1-disubstituted indolo[2,3-*a*]quinolizidines useful as vasodilators and antihypoxic agents. Further, substituted arylquinolizine derivatives, described for example in U.S. Patent No. 4,686,226 possessing alpha2-adrenoceptor antagonistic activity are useful for example as antidepressant, antihypertensive, or antidiabetic agents or platelet aggregation inhibitors. In addition, U.S. Patent No. 3,492,303 relates to indolo[2,3-*a*]quinolizidines useful as central nervous system depressants.

## SUMMARY OF THE INVENTION

An object of the present invention is to provide further antagonists of alpha2-adrenoceptors that can be used for the treatment of diseases or conditions of the peripheric or central nervous system where alpha2-antagonists are indicated to be useful. Accordingly, an object of the present invention is to provide further compounds to be used as alpha2 antagonist agents in the treatment of mammals, including humans and animals.

The invention also provides compounds useful as selective alpha2C antagonist agents for the treatment of various disorders or conditions of the central nervous system where alpha2C antagonists are indicated to be useful.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1a and b show the results from two separate locomotor activity tests where the locomotor activity of mice was tested after injections of vehicle or amphetamine (amph) (4 micromol/kg). The mice were pre-treated (20 min before amphetamine) either with vehicle, the subtype non-selective alpha2-antagonist atipamezole (1 micromol/kg) or the alpha2C-antagonists, compound 47 (3 micromol/kg)(Fig a) or compound 48 (3 micromol/kg)(Fig b). * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ compared to vehicle + amph –group (1-way ANOVA + LSD –test).

Figure 2 shows alpha2-agonist-induced sedation (measured as locomotor inhibition) in mice. The non-selective alpha2-antagonist atipamezole antagonised the sedative effects of the alpha2-subtype non-selective agonist, dexmedetomidine (Dex; 50 nmol/kg s.c.), while the alpha2C-selective antagonists did not have significant effects. (veh = vehicle). (***$p<0.001$, compared to Dex + vehicle)

Figure 3 shows the effect of the alpha2C-selective antagonists compound 47 (3 micromol/kg) and compound 48 (3 micromol/kg), the non-selective antagonist atipamezole (10 micromol/kg) and the reference antidepressants desipramine (10 micromol/kg) and fluoxetine (10 micromol/kg) in the forced swimming test in rats. All compounds, except atipamezole, increased activity (***$p<0.001$, compared to vehicle).

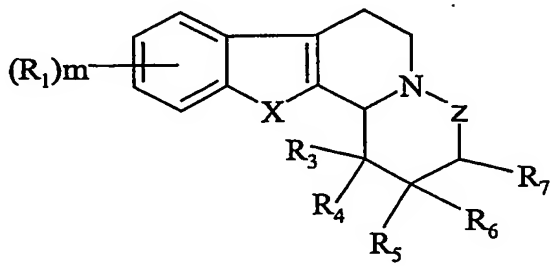
Figures 4a and 4b show the effect of compounds 47 and 48 on the startle reflex and its prepulse inhibition in rats. (Veh = vehicle). Asterisks as in Figure 1; comparisons were performed between PCP + vehicle and PCP + compounds 47 and 48.

Figures 5a and 5b show the effect of the non-selective antagonist atipamezole (ati) on the startle reflex and its prepulse inhibition in rats in the prescence of

phencyclidine (PCP); (veh = vehicle). Asterisks as in Figure 1, compared to the vehicle + PCP –group.

## DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention covers compounds of formula I:



I

wherein,

X is $CH_2$, O, S or $NR_2$;

Z is -$CHR_8$-$(CH_2)$n- or a single bond;

$R_1$ is hydroxy, $(C_1$-$C_6)$alkyl, $OCH_3$, halogen or halo$(C_1$-$C_6)$alkyl;

$R_2$ is H or $(C_1$-$C_6)$alkyl

$R_3$ is H, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_7)$cycloalkyl, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl or amino$(C_1$-$C_6)$alkyl or one of $R_3$ or $R_4$ and $R_6$ together form a bond between the ring atoms to which they are attached;

$R_4$ is H, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or hydroxy$(C_1$-$C_6)$alkyl;

$R_5$ is H, hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or hydroxy$(C_1$-$C_6)$alkyl or $R_4$ and $R_5$ form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring optionally substituted with 1 to 3 substituent(s) $R_9$ each independently being hydroxy, $(C_1$-$C_6)$alkyl, halogen, amino, nitro, $(C_3$-$C_7)$cycloalkyl, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, mono- or di$(C_1$-$C_6)$alkylamino, mono- or di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, carboxyl, $(C_1$-$C_6)$alkyl-CO-, $(C_1$-$C_6)$alkoxy-CO-, $(C_1$-$C_6)$alkoxy-CO-$(C_1$-$C_6)$alkyl or $NH_2$-CO-;

$R_6$ is H, hydroxy, ($C_1$-$C_6$)alkyl, hydroxy($C_1$-$C_6$)alkyl or $R_6$ forms a bond between the ring atom to which it is attached and the ring atom to which $R_7$ is attached;

$R_7$ is H, ($C_1$-$C_6$)alkyl or hydroxy($C_1$-$C_6$)alkyl;

$R_8$ is H or ($C_1$-$C_6$)alkyl or, only when n is 0, $R_7$ and $R_8$ form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring optionally substituted with 1 to 3 substituent(s) $R_{10}$ each independently being hydroxy, ($C_1$-$C_6$)alkyl, halogen, amino, nitro, ($C_3$-$C_7$)cycloalkyl, hydroxy($C_1$-$C_6$)alkyl, halo($C_1$-$C_6$)alkyl, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, carboxyl, ($C_1$-$C_6$)alkyl-CO-, ($C_1$-$C_6$)alkoxy-CO-, ($C_1$-$C_6$)alkoxy-CO-($C_1$-$C_6$)alkyl or $NH_2$-CO-;

$R_7$ and $R_8$ are attached to the carbon ring atoms which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or of a pharmaceutically acceptable salt or ester thereof, with the proviso, that when X is O, n is 0, $R_1$, $R_3$, $R_4$, $R_7$ and $R_8$ are hydrogen, and one of $R_5$ or $R_6$ is hydrogen, then the other $R_5$ or $R_6$ is not hydroxy($C_1$-$C_6$)alkyl.

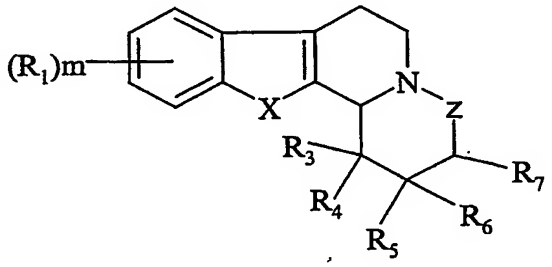
The compounds of formula I can be used for the manufacture of a medicament for the treatment of diseases or conditions where alpha2 antagonists are indicated to be effective.

In a possible subgroup of the compounds of formula I X is $NR_2$. In another possible subgroup of the compounds of formula I X is $NR_2$, $R_1$ is H, $R_3$ is ($C_1$-$C_6$)alkyl and $R_4$ is hydroxy or hydroxy($C_1$-$C_6$)alkyl.

In a further possible subgroup of the compounds of formula I the compound is 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol or 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene.

In yet another possible subgroup of the compounds of formula I X is $CH_2$, O or S.

Another embodiment of the invention provides new compounds of formula IA:



IA

wherein,

X is $CH_2$, O or S;

Z, $R_1$, $R_3$-$R_{10}$, m and n are as defined above,

or a pharmaceutically acceptable salt or ester thereof, with the provisos, that

a) when X is S and Z is a single bond or n is 0, then $R_1$ and $R_3$-$R_8$ are not all simultaneously hydrogen;

b) when X is O and n is 0, then $R_1$ and $R_3$-$R_8$ are not all simultaneously hydrogen;

c) when X is O, n is 0, $R_1$, $R_3$, $R_4$, $R_7$ and $R_8$ are hydrogen, and one of $R_5$ or $R_6$ is hydrogen, then the other $R_5$ or $R_6$ is not hydroxy($C_1$-$C_6$)alkyl.

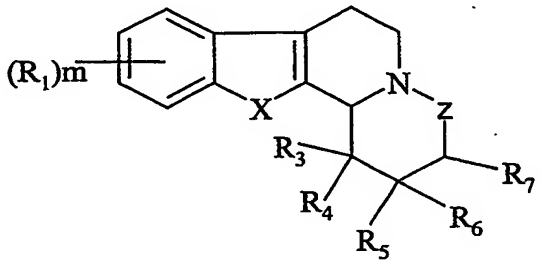
In a possible subgroup of the compounds of formula IA X is $CH_2$. In another possible subgroup of the compounds of formula IA X is O. In another possible subgroup of the compounds of formula IA X is S.

In a further possible subgroup of compounds of formula IA $R_3$ is ($C_1$-$C_6$)alkyl and $R_4$ is hydroxy or hydroxy($C_1$-$C_6$)alkyl.

In a further possible subgroup of compounds of formula IA the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol, 1α-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-

benzo[a]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol or (1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol.

Another embodiment of the invention provides new compounds of formula IB:




IB

wherein,

X is $NR_2$;

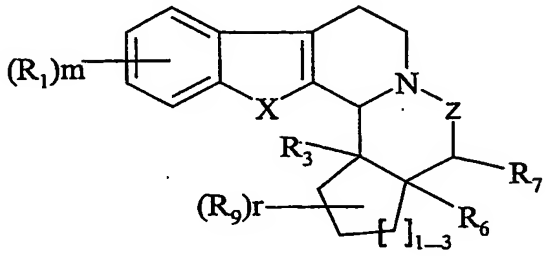
$R_2$ is $(C_1\text{-}C_6)$alkyl;

Z, $R_1$, $R_3$-$R_{10}$, m and n are as defined above,

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 2,3-Diethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-ol; 2-(1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanol; 11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indole; (11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol or (1,11-Diethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol.

In a possible subgroup of the compounds of formula IB the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol.

Another embodiment of the invention provides new compounds of formula IC:



IC

wherein,

X is $NR_2$;

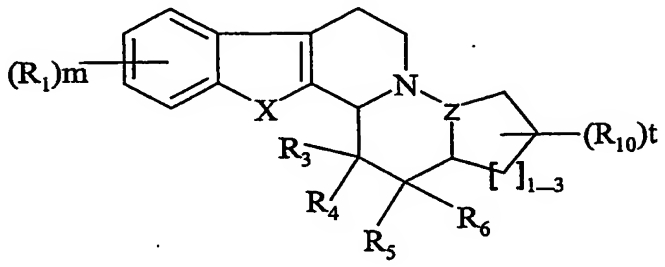
Z, $R_1$, $R_2$, $R_3$, $R_6$, $R_7$, $R_8$, $R_9$, m and n are as defined above;

r is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,7,8,13,13b,13c-Dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 5,7,7a,8,9,10,11,11a,11b,12-Decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 10-Methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-Methoxy-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-Hydroxy-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-c]phenanthrene-4-carboxylic acid methyl ester; Methyl-3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopen[a]idolizine-2-carboxylate or Methyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-g]cyclopen[a]idolizine-2-carboxylate.

In a possible subgroup of the compounds of formula IC the compound is 2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol or 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol.

Another embodiment of the invention provides new compounds of formula



ID

ID:

wherein,

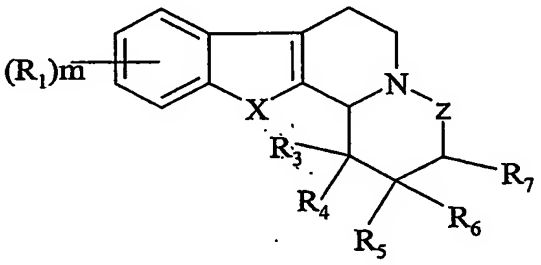
X is $NR_2$;

Z, $R_1$-$R_{10}$, m and n are as defined above;

t is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,11,11b,12,13,13a-Dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 1,2,3,4,4a,5,6,11,11b,12-Decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 9-Methoxy-1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene or 1-Hydroxy-1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene-2-carboxylicacid methyl ester.

Another embodiment of the invention provides new compounds of formula IE:



IE

wherein,

X, Z, $R_1$-$R_{10}$ and m are as defined above;

n is 1,

or a pharmaceutically acceptable salt and ester thereof, with the proviso, that the compound is not 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido-[3,4-b]indole-2-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-b]indole-2-methanol,4-ethyl; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2,3-diethyl or 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido-[3,4-*b*]indole-2-methanol.

In a possible subgroup of the compounds of formula IE the compound is 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole.

Another embodiment of the invention provides new compounds which are 2β-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 1α-ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1β-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, (1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-*n*-propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-(1α,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-butyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1-cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1α-methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3β,4α-dimethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol, and (2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol.

The terms employed herein have the following meanings:

The term "halo" or "halogen", as employed herein, refers to chlorine, bromine, fluorine or iodine.

The term "($C_1$-$C_6$)alkyl", as employed herein as such or as part of another group, refers to a straight or branched carbon chain having 1 to 6 carbon atoms. Representative examples of ($C_1$-$C_6$)alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, and the like.

The term "($C_3$-$C_7$)cycloalkyl", as employed herein, refers to a saturated cyclic hydrocarbon group containing 3 to 7 carbons. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "hydroxy", as employed herein, refers to an –OH group.

The term "hydroxy($C_1$-$C_6$)alkyl", as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through a ($C_1$-$C_6$)alkyl group, as defined herein. Representative examples of hydroxy($C_1$-$C_6$)alkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl, 1-methyl-1-hydroxypropyl, and the like.

The term "halo($C_1$-$C_6$)alkyl", as employed herein, refers to one or more halogen, as defined herein, appended to the parent molecular moiety through a ($C_1$-$C_6$)alkyl group, as defined herein. Representative examples of halo($C_1$-$C_6$)alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-bromopropyl, and the like.

The term "amino", as employed herein, refers to a $-NH_2$ group.

The term "amino($C_1$-$C_6$)alkyl", as employed herein, refers to an amino group, as defined herein, appended to the parent molecular moiety through a ($C_1$-$C_6$)alkyl group, as defined herein. Representative examples of amino($C_1$-$C_6$)alkyl include, but

are not limited to, aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 2-aminopropyl, 4-aminobutyl, 1-methyl-1-aminoethyl, and the like.

The term "mono- or di($C_1$-$C_6$)alkylamino", as employed herein, refers to one or two ($C_1$-$C_6$)alkyl group(s), as defined herein, appended to the parent molecular moiety through an amino group, as defined herein. Representative examples of mono- or di($C_1$-$C_6$)alkylamino include, but are not limited to methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino, and the like.

The term "mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl", as employed herein, refers to a mono- or di($C_1$-$C_6$)alkylamino group, as defined herein, appended to the parent molecular moiety through a ($C_1$-$C_6$)alkyl group, as defined herein. Representative examples of mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl include, but are not limited to, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylaminomethyl, *N*-methylaminoethyl, *N*-methylaminopropyl, *N*-ethyl-*N*-methylaminomethyl, and the like.

The term "($C_1$-$C_6$)alkoxy", as employed herein as such or as part of another group, refers to -O-($C_1$-$C_6$)alkyl, wherein -($C_1$-$C_6$)alkyl is as defined herein. Representative examples of ($C_1$-$C_6$)alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, and the like.

The compounds of formula I and IA, IB, IC, ID and IE, as well as the pharmaceutically acceptable salts and esters thereof, are referred to below as the compounds of the invention, unless otherwise indicated.

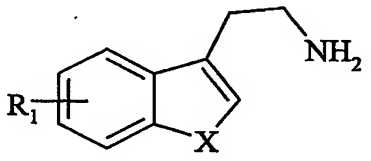
The invention includes within its scope all the possible stereoisomers of the compounds, including geometric isomers, e.g. *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers. Furthemore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods.

For the separation of optical isomers, e.g. enantiomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of those esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl esters.

The compounds of the invention can be prepared analogously or according to the methods known in the literature using suitable starting materials. The starting materials of formulae II, III and IV are commercially available or can be prepared via a variety of known synthetic routes known in the literature.

For example, the starting materials used are arylalkylamines of formula (II)

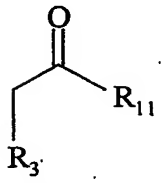



(II)

wherein $R_1$ is as defined above and X is NH, O, $CH_2$ or S.

When X is O, the amines of formula (II) can be prepared, for example, according to the process disclosed in the U.S. Patent Specification No. 4,710,504. When X is $CH_2$, the compounds of formula (II) can be prepared as described in *J. Med. Chem.* **10** (1967) 856-859. When X is S, the compounds of formula (II) can be prepared by decarboxylation of the corresponding 3-(thianaphten-3-yl)-L-alanine.

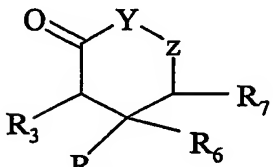
Other starting materials used are compounds of formula (III)



(III)

wherein $R_3$ is as defined above and $R_{11}$ is OH or halogen.

Furthermore, the starting materials used are compounds of formula (IV)

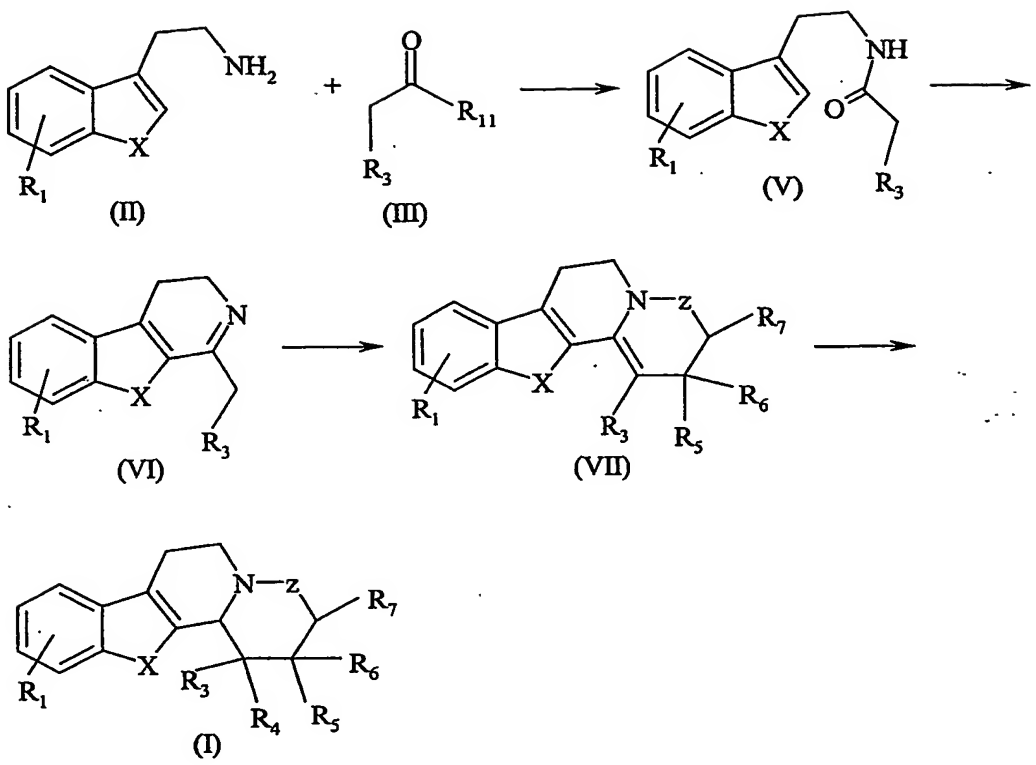


(IV)

wherein $R_3$, $R_5$-$R_7$ and Z are as defined above and Y is O or NH. Compounds of formula (IV) can be prepared according to the methods described in *Tetrahedron* **33** (1977) 1803-1808. When $R_3$ and $R_5$ form a ring, compounds of formula (IV) are obtained by the partial reduction of their corresponding anhydrides.

In general, the compounds of formula (I), wherein X is NH, O or S, can be prepared e.g. analogously or according to the following reaction scheme 1:

Scheme 1




wherein $R_1$, $R_3$-$R_7$ and Z are as defined above.

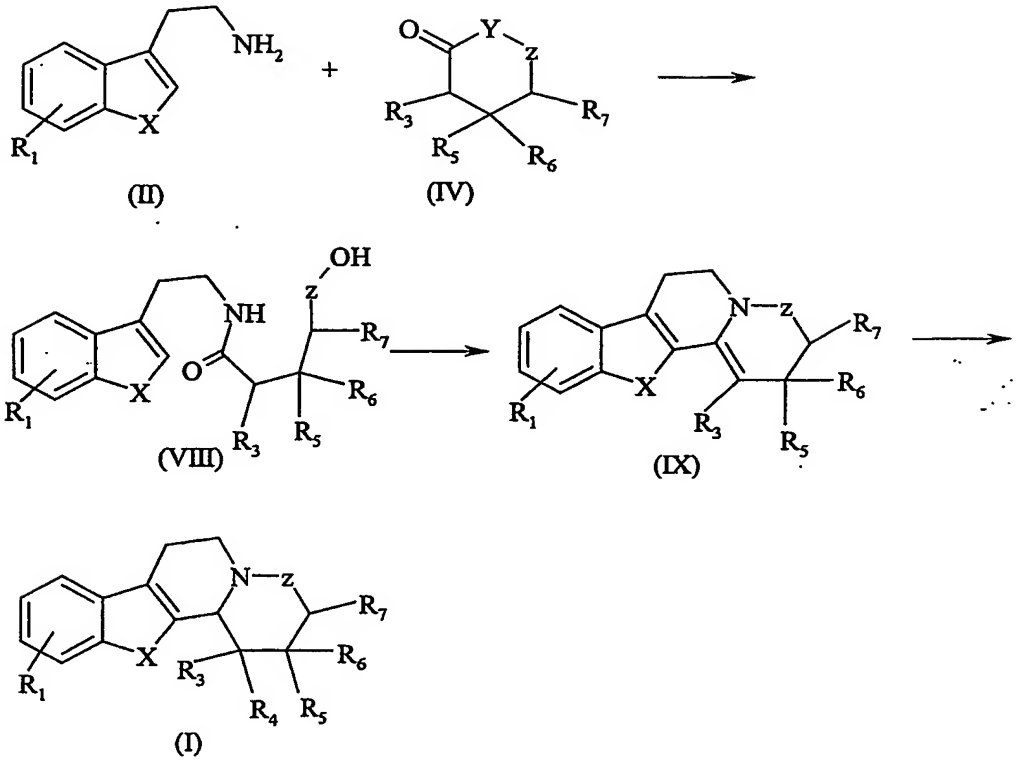
According to the reaction route of scheme I, alkylation of amines (II) with compounds of formula (III) gives amides (V) which are converted into enamines (VII) *via* beta carbolines (V) by Bischler-Napieralski reaction followed by ring D formation by allowing compounds of formula (VI) to react with 1,3-dihaloalkanes under basic conditions as described in *Gazz. Chim. Ital.* **111** (1981) 257-267. In the last step, compounds of formula (I) are obtained

1) by oxidation of enamines (VII) using potassium iodide, iodide and air or

2) by reaction of enamines (VII) with formaldehyde in presence of Hünig base at 60°C.

Another route for preparing compounds of formula (I), wherein X is $NR_2$, O, $CH_2$ or S, is illustrated in scheme 2

Scheme 2

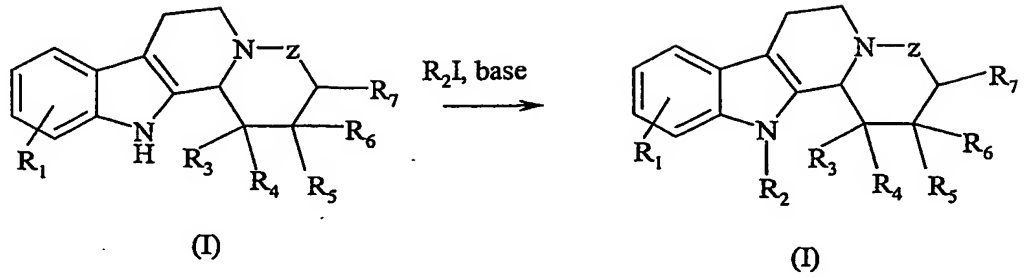



wherein X is $NR_2$, O, $CH_2$ or S, $R_1$-$R_7$ and Z are as defined above.

In scheme 2 arylalkylamines of formula (II), wherein X is NH, O, $CH_2$, or S, are reacted with compounds of formula (IV) to give amides (VIII) as described in *Tetrahedron* **33** (1977) 1803-1808. The Bischler-Napieralski cyclization of the intermediates (VIII) leads to enamines (IX) which are converted into compounds of formula (I).

The compounds of formula (I), wherein X is NH, can be alkylated with alkylhalides in the presence of a suitable base at room temperature (*Heterocycles* **27** (1988) 1179-1190) according to following scheme 3:

Scheme 3

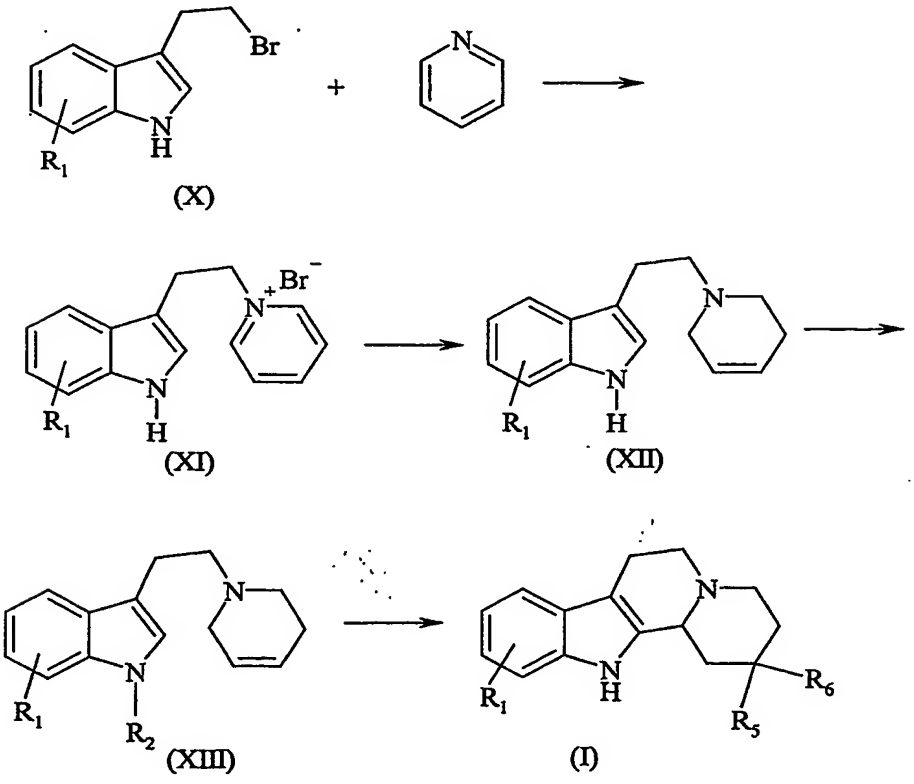



(I) (I)

wherein $R_1$-$R_7$ and Z are as defined above.

A further method for preparing compounds of formula (I) is illustrated in scheme 4:

Scheme 4

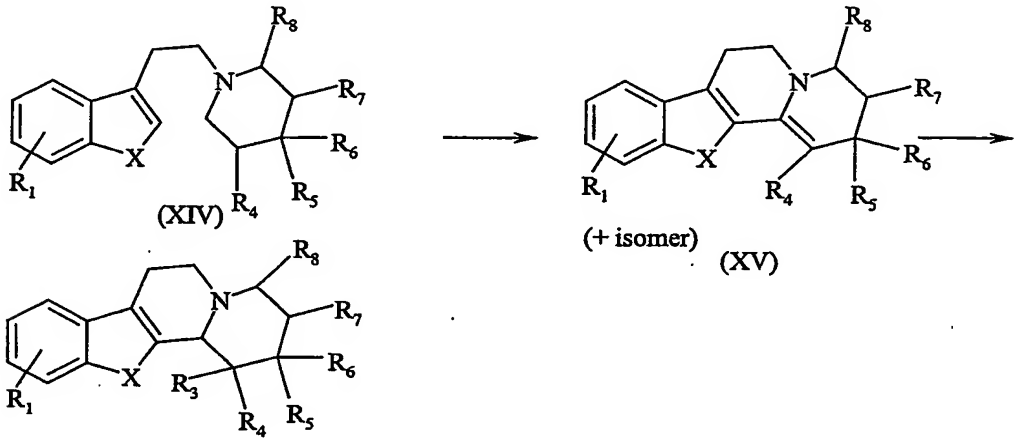



wherein $R_2$ is BOC and $R_1$, $R_5$ and $R_6$ are as defined above.

In scheme 4 pyridine is alkylated with tryptophyl bromides (X) to give pyridinium salts (XI) whose partial reduction gives compounds of formula (XII). Protection of compounds of formula (XII) using di-*t*-butyl dicarbonate under basic conditions gives compounds of formula (XIII). The Polonovski-Potier reaction of the obtained intermediates and their cyclisation using MeOH/HCl yield the compounds of formula (I).

A further process for the preparation of compounds of formula (I), wherein X is O, S or NH, $R_1$ and $R_3 - R_8$ are as defined above, is shown in the following scheme 5:

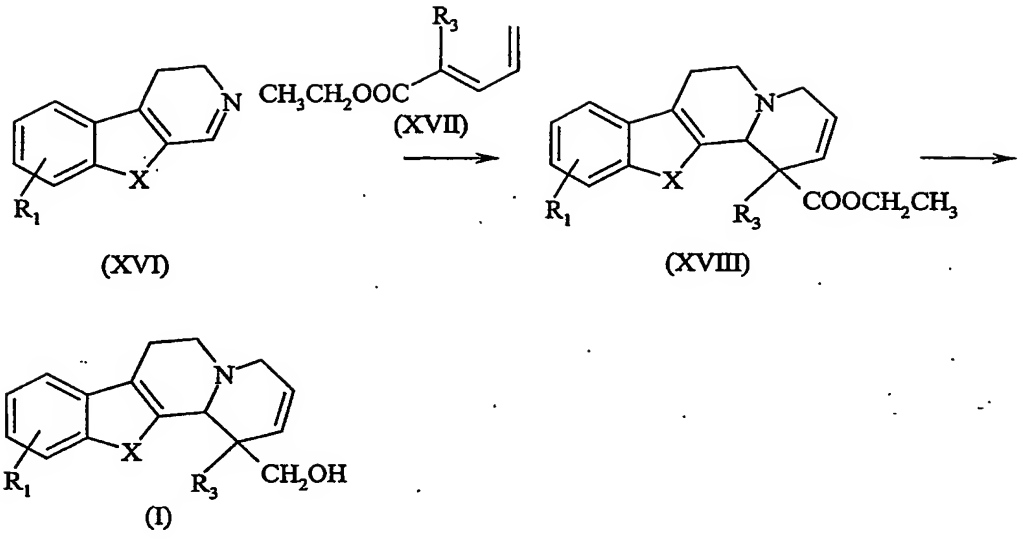
Scheme 5




In scheme 5 oxidative cyclization of derivative (XIV) with mercuric acetate according to the method described in *Heterocycles* **32** (1991) 489-497 gives enamine (XV). This intermediate can be oxidized or treated with formaldehyde as in scheme 1 or reduced with sodium borohydride to give compounds of formula (I).

A further method for preparing compounds of formula (I), wherein $R_6$ and $R_7$ form a bond, is illustrated in scheme 6:

Scheme 6

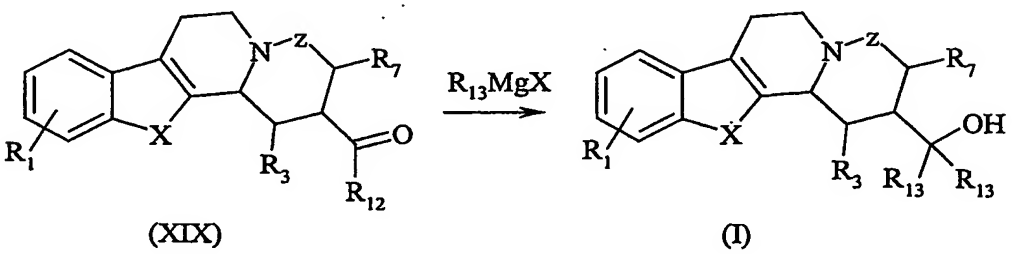



wherein X is NH and $R_3$ is lower alkyl.

Applying the method described in *J. Org. Chem.* **52** (1987) 353-356, the hetero-Diels-Alder reaction of 3,4-dihydro-β-carboline (XVI) with diene ester (XVII), prepared by the Wittig reaction as described in *Can. J. Chem.* **65** (1987) 670-682, gives compounds of formula (XVIII), which are then reduced to alcohols of formula (I).

A further method for preparing compounds of formula (I) is illustrated in scheme 7.

Scheme 7

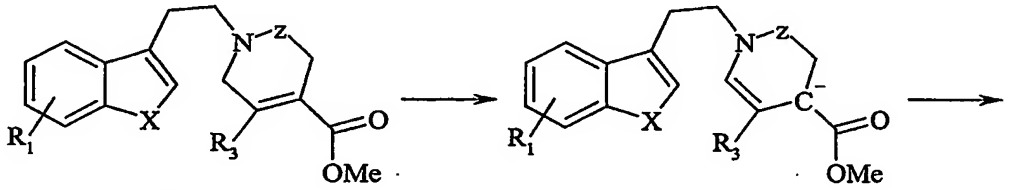


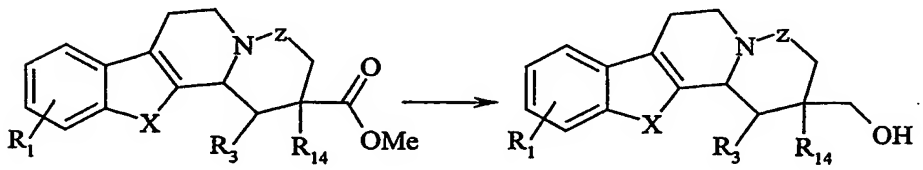
wherein X, $R_1$, $R_3$, $R_7$ and z are as defined above. $R_{12}$ can be H or $OCH_3$ and $R_{13}$ can be an alkyl or aryl group.

In scheme 7, compounds of formula (XIX), when $R_{12}$ is H, are prepared as described in *J. Chem. Soc., Chem. Commun.* (1995) 2317-2318, and compounds of formula (XIX), when $R_{12}$ is $OCH_3$, are prepared as described in *J. Chem. Soc. (C)* (1971) 736-743. Compounds of formula (XIX) are reacted with Grignard reagents to give compounds of formula (I). When $R_{12}$ in formula (XIX) is H, the other $R_{13}$ group in formula (I) is also H.

A new method to prepare certain compounds of formula (I) is shown in scheme 8.

Scheme 8




wherein X, $R_1$, $R_3$ and z are as defined above. $R_{14}$ is a lower alkyl group.

In scheme 8 tetrahydropyridine (XX), prepared according to the method described in *J. Chem. Soc. (C)* (1971) 736-743, is deprotonated with a strong base to give anion (XXI). This anion was alkylated and subsequently cyclized with acid to give compounds of formula (XXII). Reduction of (XXII) with $LiAlH_4$ then affords compounds of formula (I).

The resolution of the racemic compounds of formula (I) can be performed, for example, by converting compounds of formula (I) into their diastereoisomers salt mixture by reaction with an optically active acid such as D-tartaric acid, dibenzoyl-D-tartaric acid, etc and by separation of the diastereoisomers by crystallization.

It is obvious to a skilled person that, in the above reactions, any starting material or intermediate can be protected, if necessary, in manner well known in the chemical field. Any protected functionality is subsequently deprotected in a usual manner.

It should be noted that the above described synthetic routes are meant to illustrate the preparation of the compounds of the invention and the preparation is by no means limited thereto, i.e. other synthetic methods which are within the general knowledge of a skilled person are also possible.

The compounds of the invention may be converted, if desired, into their pharmaceutically acceptable salt or ester form using methods well known in the art.

The present invention will be explained in more detail by the following examples. The examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

**EXAMPLE 1**

**1-Propyl-4,9-dihydro-3H-beta-carboline**

8.00 g (50.0 mmol) of tryptamine was dissolved in 150 ml of ethyl acetate and 4.80 ml (52.0 mmol) of *n*-butyric acid was slowly added. After standing for 4 hours at 0°C, the reaction mixture was filtered to give 12.30 g (49.5 mmol) of tryptamine butyrate, which was melted. The melt was heated at 200°C and kept for 30 min at that temperature. Water formed was removed using Dean-Stark apparatus. The melt after cooling was mixed with 120 ml of toluene, 23.5 ml (257.7 mmol) of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 4 hours. The solution was evaporated in vacuum and the dark oil was mixed with 20 % solution of acetic acid (3 x 50 ml). The solid was filtered off and the aqueous solution was made alkaline with 25 % ammonium hydroxide under cooling and extracted with dichloromethane (3 x 50 ml). The combined organic

phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR**: 1.00 (t, 3H), 1.75 (m, 2H), 2.66 (t, 2H), 2.87 (t, 2H), 3.90 (t, 2H), 7.00-7.62 (m, 4H), 8.94 (br s, 1H).

**MS**: 212 (28%), 211 (12%), 197 (25%), 184 (100%), 169 (13%).

**EXAMPLE 2**

**1-Isobutyl-4,9-dihydro-3H-beta-carboline**

The procedure of example 1 was repeated, except that isovaleric acid was used instead of *n*-butyric acid.

**NMR**: 0.98 (d, 6H), 2.16 (m, 1H), 2.54 (d, 2H), 2.86 (t, 2H), 3.89 (t, 2H), 7.00-7.62 (m, 4H), 8.60 (br s, 1H).

**MS**: 226 (16%), 211 (18%), 184 (100%), 169 (13%).

**EXAMPLE 3**

**1-Butyl-4,9-dihydro-3H-beta-carboline**

The procedure of example 1 was repeated, except that *n*-valeric acid was used instead of *n*-butyric acid.

**NMR**: 1.00 (t, 3H), 7.00-7.62 (m, 4H), 8.64 (br s, 1H).

**MS**: 226 (18%), 211 (18%), 184 (100%), 169 (14%).

**EXAMPLE 4**

**1-(2-Methyl-butyl)-4,9-dihydro-3H-beta-carboline**

The procedure of example 1 was repeated, except that 3-methylvaleric acid was used instead of *n*-butyric acid.

**NMR**: 0.84 (t, 3H), 0.87 (d, 3H), 7.05-7.60 (m, 4H), 12.2 (br s, 1H).

**MS**: 240 (9%), 225 (10%), 211 (10%), 185 (13%), 184 (100%), 183 (14%), 155 (24%).

**EXAMPLE 5**

**1-Cyclohexylmethyl-4,9-dihydro-3H-beta-carboline**

The procedure of example 1 was repeated, except that cyclohexylacetic acid was used instead of *n*-butyric acid.

**NMR**: 1.0-1.9 (m, 11H), 2.56 (d, 2H), 2.85 (m, 2H), 3.88 (m, 2H), 7.14-7.63 (m, 4H), 8.55 (br s, 1H).

**MS**: 266 (8%), 185 (15%), 184 (100%), 183 (12%), 155 (17%).

**EXAMPLE 6**

**1β-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 1)

2.56 g (11.5 mmol) of 4,9-Dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole (example 2), 2 ml of *N*-ethyldiisopropylamine, and 1.35 ml (13.8 mmol) of 1-bromo-3-chloropropane were dissolved in 50 ml of acetonitrile. The mixture was refluxed under argon for 8 hours. After evaporation of the solvent, 20 ml of methanol and 1.3 g (34.5 mmol) of sodium borohydride were added. The reaction mixture was stirred for 1 hour at room temperature and 20 ml of water was then added. The reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR**: 1.02 (br s, 6H), 7.11 (t, 1H), 7.18 (t, 1H), 7.35 (d, 1H), 7.48 (d, 1H), 7.85 (br s, 1H).

**MS**: 267 (100%), 253 (20%), 197 (35%), 170 (30%), 169 (30%).

**EXAMPLE 7**

**2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol** (Compound 2)

To a solution of 190 mg (0.7 mmol) of 1-(1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolozin-1-yl)-ethanone (*Tetrahedron Lett.* **30** (1989) 719-722.) in 5 ml of dichloromethane at –60° C was added 0.11 ml (0.8 mmol) of ethylmagnesium bromide (1.0 *M*). The reaction mixture was stirred 30 min at that temperature and 2 hours at room temperature. Water (10 ml) was then added and the reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR**: 0.97 (t, 3H), 1.30 (s, 3H), 4.69 (br s, 1H), 7.00-7.50 (m, 4H), 8.36 (br s, 1H).

**MS**: 297 (100%), 281 (30%), 269 (35%), 225 (28%), 197 (45%), 170 (35%), 169 (34%).

**EXAMPLE 8**

**2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol** (Compound 3)

The procedure of example 7 was repeated, except that methylmagnesium bromide (excess) was used instead of ethylmagnesium bromide.

**NMR**: 1.37 (s, 3H), 1.42 (s, 3H), 4.73 (br s, 1H), 7.00-7.50 (m, 4H), 8.18 (br s, 1H).

**MS**: 283 (100%), 267 (42%), 225 (33%), 197 (60%), 170 (50%), 169 (50%).

**EXAMPLE 9**

**1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 4)

5.13 g (23.0 mmol) of 4,9-Dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole, 4 ml of *N*-ethyldiisopropylamine, and 2.7 ml (27.6 mmol) of 1-bromo-3-chloropropane were dissolved in 100 ml of acetonitrile. The mixture was refluxed under argon for 8 hours. The dark solution was concentrated to the oil, which was treated with 20% sodium hydroxide. After stirring for 10 min, the solution was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the corresponding enamine, which was dissolved in 100 ml of acetonitrile. 7.0 g (27.6 mmol) of iodine and 4.6 g (27.6 mmol) of potassium iodide were added. The reaction mixture was stirred in the dark under air during 3 hours. After evaporation of the solvent, 50 ml of methanol and 2.6 g (69 mmol) of sodium borohydride were added. The reaction mixture was stirred for 1 hour at room temperature and 20 ml of water was then added. The reaction mixture was extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR**: 0.47 (d, 3H), 0.90 (d, 3H), 3.48 (br s, 1H), 7.00-7.50 (m, 4H), 8.92 (br s, 1H).

**MS**: 284 (14%), 239 (13%), 171 (100%), 170 (16%), 169 (33%).

**EXAMPLE 10**

**1α-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 5)

The procedure of example 9 was repeated, except that 4,9-dihydro-1-propyl-3-*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole and 1, 3 dibromobutane was used instead of 1-bromo-3-chloropropane.

**NMR**: 0.69 (t, 3H), 1.00 (d, 3H), 3.20 (br s, 1H), 7.00-7.60 (m, 4H), 9.04 (br s, 1H).

**MS**: 284 (5%), 267 (15%), 225 (100%), 210 (15%), 195 (15%), 182 (72%), 171 (41%), 170 (22%), 169 (32%).

**EXAMPLE 11**

**9-Fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 6)

The procedure of example 9 was repeated, except that 6-fluoro-1-isobutyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (prepared from 5-fluorotryptamine as described in example 2) was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

**NMR**: 0.45 (d, 3H), 0.89 (d, 3H), 3.32 (s, 1H), 6.8-7.25 (m, 3H), 8.94 (br s, 1H).

**MS**: 302 (26%), 203 (13%), 189 (100%), 161 (26%).

**EXAMPLE 12**

**1-*s*-Butyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (mixture of isomers) (Compound 7)

The procedure of example 9 was repeated, except that 1-(2-methylbutyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

**NMR**: 0.48 (d, 3H, major isomer), 0.69 (t, 3H, minor isomer), 0.82 (t, 3H, major isomer), 0.92 (d, 3H, minor isomer), 3.30 (s, 1H), 7.0-7.5 (m, 4H), 8.88 (br s, 1H, minor isomer), 8.93 (br s, 1H, major isomer).

**MS**: 298 (23%), 172 (24%), 171 (100%), 170 (15%), 169 (23%), 143 (29%).

**EXAMPLE 13**

**1-Cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 8)

The procedure of example 9 was repeated, except that 1-cyclohexylmethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

**NMR**: 3.35 (br s, 1H), 7.02-7.55 (m, 4H), 8.98 (br s, 1H).

**MS**: 324 (21%), 172 (12%), 171 (100%), 170 (10%), 169 (15%), 143 (22%).

**EXAMPLE 14**

**(1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 9)

The procedure of example 9 was repeated, except that instead of oxidation using iodine and potassium iodide, the enamine obtained was treated with 40 % aqueous formaldehyde and the reaction mixture was heated to reflux for 3 hours and the solvent was evaporated. The residue was diluted with ethylacetate and washed with brine. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane / methanol, 98:2).

**NMR**: 0.58 (br s, 3H), 0.82 (d, 3H), 3.07 (br s, 1H), 3.62 (d, 1H), 4.13 (d, 1H), 7.00-7.50 (m, 4H), 9.41 (br s, 1H).

**MS**: 298 (100%), 297 (55%), 281 (60%), 170 (75%), 169 (52%).

**EXAMPLE 15**

**(1α- *n*-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 10)

The procedure of example 14 was repeated, except that 4,9-Dihydro-1-butyl-3-*H*-pyrido[3,4-*b*]indole was used instead of 4,9-dihydro-1-isobutyl-3-*H*-pyrido[3,4-*b*]indole.

**NMR**: 0.81 (t, 3H), 3.34 (br s, 1H), 3.65 (d, 1H), 3.82 (d, 1H), 7.00-7.50 (m, 4H), 10.07 (br s, 1H).

**MS**: 298 (100%), 297 (65%), 281 (67%), 170 (75%), 169 (52%).

**EXAMPLE 16**

**(1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 11)

The procedure of example 14 was repeated, except that 1-ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole was used instead 4,9-dihydro-1-isobutyl-3*H*-pyrido[3,4-*b*]indole.

**NMR**: 0.91 (s, 3H), 3.37 (br s, 1H), 3.70 (d, 1H), 3.76 (d, 1H), 7.0-7.6 (m, 4H), 9.78 (br s, 1H).

**MS**: 270 (97%), 269 (100%), 253 (53%), 197 (48%), 170 (68%), 169 (62%).

**EXAMPLE 17**

**(1α-Ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 12)

A mixture of 0.34 g (2.0 mmol) of 3,4-dihydro-β-carboline and 0.39 g (2.5 mmol) of 2-ethyl penta-2,4-dienoic acid ethyl ester in 5 ml of chlorobenzene was refluxed for 16 h. The solvent was evaporated and the residue was subjected to column chromatography (silica gel, dichloromethane/methanol, 99:1) to give the ester intermediate. This product was reduced in the usual manner with lithium aluminum hydride in dry tetrahydrofuran to afford the title compound.

**NMR**: 0.82 (t, 3H), 3.69 (d, 1H), 3.70 (br s, 1H), 3.90 (d, 1H), 5.42 (ddd, 1H), 5.97 (ddd, 1H), 7.0-7.5 (m, 4H), 10.02 (br s, 1H).

**MS**: 282 (31%), 171 (14%), 170 (100%), 169 (52%).

**EXAMPLE 18**

**2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine** (Compound 13) **and**

**2α-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine** (Compound 14)

1.16 g (14.7 mmol) of pyridine and 3.0 g (13.4 mmol) of tryptophyl bromide were dissolved in 15 ml of dry ether. The reaction mixture was heated with stirring at 60°C until complete evaporation of the solvent. The mixture was then heated at 100°C for 2 hours to give the corresponding pyridinium bromide salt, which was

dissolved in 100 ml of methanol. 1.52 g (40.1 mmol) of sodium borohydride was added slowly with cooling. The reaction mixture was stirred at room temperature for 4 hours. 20 ml of water was then added. The reaction mixture was extracted with dichloromethane (3 x 30 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated. The residue was dissolved in 100 ml of abs dichloromethane. 2.91 g (13.3 mmol) of di-*t*-butyl dicarbonate and 1.49 g (1.2 mmol) of DMAP were added. The reaction mixture was stirred at room temperature under argon atmosphere. After 2h the mixture was evaporated and purified by column chromatography (silica, $CH_2Cl_2$/MeOH, 98:2). The obtained viscous oil was dissolved in 40 ml of dichloromethane and 2.54 g (13.3 mmol) of *m*CPBA was added. The solution was stirred for 2h at 0°C after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 98:2) to yield the Boc $N_b$-oxides.

In a stirring solution of 0.59 g (1.7 mmol) of Boc $N_b$-oxide in 15 ml of dichloromethane at 0°C was slowly added 3.0 ml of trifluoroacetic anhydride (TFAA). The cold bath was removed and the stirring was continued for 2 h at rt after which the reaction mixture was evaporated. 20 ml of MeOH, saturated with HCl, was added and the mixture was refluxed for 2h. Alkaline work-up and purification by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 98:2) yielded:

2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine

**NMR**: 1.54 (ddd, 1H), 3.24 (dd, 1H), 3.38 (dddd, 1H), 3.43 (s, 3H), 7.00-7.50 (m, 4H), 7.77 (br s, 1H).

**MS**: 256 (100%), 255 (86%), 255 (59%), 197 (35%), 169 (30%).

and 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine

**NMR**: 3.41 (s, 3H), 3.67 (br s, 1H), 3.68 (br d, 1H), 7.00-7.50 (m, 4H), 7.72 (br s, 1H).

**MS**: 256 (100%), 255 (75%), 255 (70%), 223 (45%), 197 (40%), 170 (45%), 169 (65%).

**EXAMPLE 19**

**1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol** (Compound 15)

To a solution of 0.086 g (0.3 mmol) of 1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine-2-carbaldehyde (*J. Chem. Soc. Chem. Commun.* **22** (1995) 2317-2318) dissolved in 2 ml of dichloromethane at –60 °C was added 0.22 ml (1.7 mmol) of 1M ethylmagnesium bromide. The reaction mixture was stirred for 4h under argon. Work-up with aqueous sodium hydroxide, followed by extraction with dichloromethane, and purification by column chromatography (silica, dichloromethane/methanol, 98:2) gave the title compound.

**NMR**: 1.02 (t, 3H), 1.93 (br d, 1H), 2.30 (br d, 1H), 6.80-7.40 (m, 4H).

**MS**: 284 (95%), 283 (100%), 225 (80%), 169 (36%).

**EXAMPLE 20**

**(1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol** (Compound 16)

To a solution of 88 mg (0.31 mmol) of 1,2α,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]-quinolizine-2-carboxylic acid methyl ester in 3 ml of dry tetrahydrofuran was added dropwise 1 ml (3.0 mmol) of a solution of methylmagnesium chloride (3M in tetrahydrofuran). The resulting solution was then refluxed for 90 min. The mixture was then worked-up as in example 7 to give the crude alcohol, which was purified by column chromatography (silica gel, dichloromethane/methanol, 95:5) to give the title compound.

**NMR**: 1.20 (s, 3H), 1.25 (s, 3H), 3.28 (br d, 1H), 7.0-7.5 (m, 4H).

**MS**: 284 (86%), 283 (65%), 225 (100%).

**EXAMPLE 21**

**(1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol** (Compound 17)

As in example 20, 64 mg (0.23 mmol) of 1,2α,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]-quinolizine-2-carboxylic acid methyl ester in 3 ml of dry tetrahydrofuran and 0.7 ml (2.1 mmol) of a solution of methylmagnesium chloride (3M in tetrahydrofuran) were refluxed for 90 min. Work-up as above gave, after column chromatography (silica gel, dichloromethane/methanol, 90:10), the title compound.

NMR: 1.17 (s, 3H), 1.18 (s, 3H), 4.57 (br s, 1H), 7.0-7.5 (m, 4H), 8.65 (br s, 1H).

MS: 284 (58%), 283 (53%), 225 (100%).

**EXAMPLE 22**

**(2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol** (Compound 18)

To a stirred solution of 0.36 g (3.6 mmol) of diisopropylamine in 4 ml of dry tetrahydrofuran at -50°C was added 2.0 ml (3.6 mmol) of n-butyl lithium (1.8 M in hexanes). The mixture was allowed to warm up to -30°C (15 min), after which it was cooled to -70°C. At this temperature, 0.64 g (3.6 mmol) of hexamethylphosphoramide was added. Stirring was continued for 30 min at this temperature, after which 0.42 g (1.48 mmol) of methyl 1-[2-(3-indolyl)ethyl]-1,2,5,6-tetrahydropyridine-4-carboxylate in 7 ml of tetrahydrofuran was added. After stirring for 20 min still at -70°C, the mixture was allowed to warm up to -40°C (15 min). At this temperature, 0.3 g (3.6 mmol) of ethyl iodide was added and stirring was continued for 1 h. The cooling bath was then removed and, after additional 15 min, the mixture was quenched with 5% ammonia. The aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were washed with water. Drying over sodium sulfate, filtration and evaporation of the solvent gave the crude enamine, which was dissolved in 50 ml of methanol saturated with hydrogen chloride and the resulting solution was stirred for 16 h at room temperature. The solvent was evaporated and the residue was treated with aqueous sodium hydrogen carbonate. After normal extraction procedures (dichloromethane), the solvent was evaporated to give the crude product, which was subjected to column chromatography (silica gel, dichloromethane/methanol, 98:2) to afford the intermediate ester, 2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester. This compound was then treated with $LiAlH_4$ in dry tetrahydrofuran in the usual manner to give, after column chromatography (silica gel, dichloromethane/methanol, 95:5), the title alcohol.

NMR: 0.90 (t, 3H), 3.29 (d, 1H), 3.43 (d, 1H), 3.52 (br d, 1H), 7.0-7.5 (m, 4H).

**MS**: 284 (100%), 283 (98%), 253 (33%), 197 (37%), 170 (33%), 169 (40%), 156 (34%).

**EXAMPLE 23**

**(2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol** (Compound 19)

A solution of 51 mg (0.16 mmol) of the ester intermediate obtained in example 33 (2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester) in 4 ml of trifluoroacetic acid was refluxed under argon for 16 h. The acid was evaporated and the residue treated with aqueous sodium hydrogen carbonate. After normal extraction procedures (dichloromethane) a crude mixture (20:80) of the two diastereomers, 2α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester and 2α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-2-carboxylic acid methyl ester, was obtained. The latter isomer was separated by column chromatography (silica gel, dichloromethane/methanol, 99:1) and it was then reduced in the usual way with $LiAlH_4$ in dry tetrahydrofuran. Purification as above (silica gel, dichloromethane/methanol, 95:5) then gave the title alcohol.

**NMR**: 0.87 (t, 3H), 3.51 (d, 1H), 3.78 (d, 1H), 7.0-7.5 (m, 4H).

**MS**: 284 (95%), 283 (100%), 253 (30%), 197 (30%), 170 (17%), 169 (23%), 156 (19%).

**EXAMPLE 24**

**2,3,4,5,7,8,13,13b-octahydro-1H-Azepino[1',2':1,2]pyrido[3,4-*b*]indole** (Compound 20)

To a solution of 0.20 g (1.2 mmol) of tryptamine in 5.0 ml of xylene was added 0.14 g (1.2 mmol) of that ε-caprolactam. The mixture was refluxed for 7 hours. After evaporation of the solvent, the residue was dissolved in 5.0 ml of toluene and 0.65 ml of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 9 hours. The solution was evaporated in vacuum and the obtained residue was mixed with 20 % solution of acetic acid (3 x 10 ml). The solid was filtered off and the aqueous solution was made alkaline (pH 11) with 25 % ammonium hydroxide under cooling and extracted with dichloromethane (3 x

20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and 6.0 ml of 4M sodium hydroxide was added to the filtrate. The mixture was refluxed for 1 hour. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated to give oil, which was dissolved in 30 ml of methanol. To the cold solution was added 0.2 g (5.6 mmol) of sodium borohydride. The mixture was stirred at room temperature for 1 hour. Water was slowly added. The reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate and the drying agent was filtered off to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR:** 4.03 (br d, 1H), 7.11-7.46 (m, 4H), 8.05 (br s, 1H).

**MS:** 240 (52%), 239 (100%), 198 (10%), 170 (24%).

**EXAMPLE 25**

**1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 21)

To a solution of 0.05 g (0.1 mmoles) of 1α-ethyl-1β-hydroxy-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine and 0.05 g (0.9 mmoles) of KOH in 1.0 ml of acetone was added 0.02 ml (0.3 mmoles) of iodomethane. The reaction mixture was stirred at rt for 1 hour. Water was slowly added and the reaction mixture was extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 95:5).

**NMR**: 0.71 (t, 3H), 1.01 (m, 2H), 3.59 (br s, 1H), 3.72 (s, 3H), 7.00-7.50 (m, 4H).

**MS**: 284 (21%), 283 (100%), 185 (60%), 170 (10%).

**EXAMPLE 26**

**1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 22)

The procedure of example 25 was repeated, except that iodoethane was used instead of iodomethane.

**NMR**: 0.71 (t, 3H), 1.00 (m, 2H), 1.07 (t, 3H), 3.60 (s, 1H), 4.20 (m, 1H), 4.64 (m, 1H), 7.00-7.50 (m, 4H).

**MS**: 298 (29%), 297 (19%), 199 (100%), 171 (33%).

**EXAMPLE 27**

**1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol** (Compound 23)

To a solution of 0.48 g (3.0 mmol) of 2-(3-benzo[b]furanyl)ethylamine in 5.0 ml of xylene was added 0.34 g (3.0 mmol) of 1-methyl-δ-valerolactone. The mixture was refluxed for 7.5 hours. After evaporation of the solvent the residue was dissolved in 6.0 ml of toluene and 0.72 ml of freshly distilled phosphorus oxychloride was added and the reaction mixture was refluxed for 11 hours. The solution was evaporated in vacuum and the obtained oil was mixed with 20 % solution of acetic acid (3 x 20 ml). The solid was filtered off and the aqueous solution was made alkaline (pH 11) with 25 % ammonium hydroxide under cooling and extracted with dichloromethane (3 x 20 ml). The combined organic phases were dried over sodium sulfate and the drying agent was filtered off. To the filtrate was added 12.5 ml of 4M sodium hydroxide. The mixture was refluxed for 1 hour. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was concentrated to give the corresponding enamine, which was oxidised as described in example 9.

**NMR**: 1.18 (s, 3H), 3.25 (br d, 1H), 7.10-7.50 (m, 4H).

**MS**: 257 (25%), 242 (10%), 172 (100%).

**EXAMPLE 28**

**(1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol** (Compound 24)

The procedure of example 27 was repeated, except that to the formed enamine, 40 % aqueous formaldehyde was slowly added. The reaction mixture was refluxed for 3.5 hours and the solvent was evaporated. The residue was diluted with ethylacetate and washed with brine. The organic phase was dried over sodium sulfate, the drying agent was filtered off and the filtrate was evaporated to give the title compound, which was purified by column chromatography (dichloromethane/methanol, 98:2).

**NMR**: 0.89 (s, 3H), 3.40 (br s, 1H), 3.62 (d, 1H), 4.29 (d, 1H), 7.10-7.50 (m, 4H).

**MS**: 271 (69%), 270 (100%), 198 (45%), 171 (52%), 170 (60%).

**EXAMPLE 29**

**1α-Isopropyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol** (Compound 25)

The procedure of example 9 was repeated, except that 2-(3-benzo[b]furanyl)ethylamine was used instead of tryptamine.

**NMR**: 1.00 (m, 6H), 7.25 (m, 2H), 7.44 (m, 2H),

**MS**: 285 (23%), 242 (10%), 198 (10%), 186 (23%), 172 (100%).

**EXAMPLE 30**

**1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol** (Compound 26)

The procedure of example 27 was repeated, except that 1-ethyl-δ-valerolactone was used instead of 1-methyl-δ-valerolactone.

**NMR**: 0.73 (t, 3H), 3.22 (br s, 1H), 7.00-7.30 (m, 2H), 7.40-7.55 (m, 2H).

**MS**: 271 (15%), 186 (18%), 173 (11%), 172 (100%), 170 (28%).

**EXAMPLE 31**

**(1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol** (Compound 27)

The procedure of example 28 was repeated, except that 1-ethyl-δ-valerolactone was used instead of 1-methyl-δ-valerolactone.

**NMR**: 0.62 (t, 3H), 3.48 (br s, 1H), 3.52 (d, 1H), 4.06 (d, 1H), 7.00-7.30 (m, 2H), 7.40-7.55 (m, 2H).

**MS**: 285 (56%), 284 (100%), 268 (19%), 198 (36%), 172 (20%), 171 (44%), 170 (54%).

**EXAMPLE 32**

**5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol** (Compound 28)

The procedure of example 27 was repeated, except that instead of 2-(3-benzo[b]furanyl)ethylamine and 1-methyl-δ-valerolactone, tryptamine and hexahydroisobenzofuran-1-one were used.

**NMR**: 4.45 (br d, 1H), 7.00-7.60 (m, 4H), 9.11 (br s, 1H).

**MS**: 296 (8%), 143 (100%), 130 (81%).

**EXAMPLE 33**

**1,2,3,4,4a,5,6,7,8,13-Decahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene**

To a solution of 0.356 g (1.26 mmol) of *N*-[2-(3-indolyl)ethyl)]decahydroisoquinoline in 20 ml of ethanol was added a solution of 1.6 g of mercuric acetate and 1.88 g of ethylenediaminetetra-acetic acid disodium salt dihydrate in 40 ml of water and the resulting mixture was refluxed for 3 h. The cooled mixture was made basic with dilute ammoniumhydroxide (pH 11) and then extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over sodium sulfate, filtered and the solvent evaporated to give the crude enamine (mixture of isomers), which was directly used in the next step (see example 34). The pure enamine could be obtained by column chromatography on silica gel using dichloromethane/methanol/triethylamine (98:1:1) as eluent.

**EXAMPLE 34**

**2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol** (Compound 29)

As in example 9, 0.42 g (1.51 mmol) of the crude enamine from example 33 was treated with 0.21 g of potassium iodide and 0.32 g of iodine in 30 ml of acetonitrile. After reduction with 0.29 g of sodium borohydride in 30 ml of methanol, the crude product was purified by column chromatography (silica, dichloromethane/methanol, 99:1) to afford the pure alcohol.

**NMR**: 3.18 (br s, 1H), 7.0-7.55 (m, 4H), 9.18 (br s, 1H).

**MS**: 296 (25%), 295 (10%), 185 (15%), 171 (100%).

**EXAMPLE 35**

**(2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol** (Compound 30)

150 mg (1.51 mmol) of the pure enamine (from example 33) was refluxed for 3 h with 2 ml of 36% aqueous formaldehyde and 0.2 ml *N*-ethyldiisopropylamine in 10 ml of acetonitrile. After work-up the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 98:2) to afford the pure alcohol.

**NMR**: 3.29 (br s, 1H), 3.98 (d, 1H), 4.17 (d, 1H), 7.0-7.5 (m, 4H), 10.05 (br s, 1H).

**MS**: 310 (88%), 309 (100%), 293 (34%), 197 (67%), 184 (35%), 170 (90%), 169 (77%).

**EXAMPLE 36**

**3β,4α-Dimethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 31)

To a solution of 0.422 g (1.65 mmol) of *N*-[2'-(3'-indolyl)ethyl)]-2,3-dimethylpiperidine in 25 ml of ethanol was added 2.1 g of mercuric acetate and 2.46 g of ethylenediaminetetraacetic acid disodium salt dihydrate in 50 ml of water and the resulting mixture was refluxed for 3 h. The cooled mixture was made basic with dilute ammoniumhydroxide and then extracted with dichloromethane. Drying over sodium sulfate, filtration and evaporation of the solvent gave the crude enamine, which was dissolved in 30 ml methanol and cooled with an ice bath. A few drops of acetic acid were added followed by 0.322 g of sodium borohydride in portions. After stirring for 1.5 h the mixture was worked up in the usual manner to give the crude product, which was purified by column chromatography on silica gel using dichloromethane/methanol (98.5:1.5) as eluent.

**NMR**: 0.89 (d, 3H), 0.96 (d, 3H), 3.76 (br d, 1H), 7.0-7.5 (m, 4H), 7.71 (br s, 1H).

**MS**: 254 (95%), 253 (100%), 239 (30%), 170 (31%), 169 (36%).

**EXAMPLE 37**

**Resolution of 1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 4)

A solution of 0.3 g (1.1 mmol) of (±)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol and 0.16 g (1.1 mmol) of L-tartaric acid in 15 ml of acetone was refluxed for 30 min. On standing at room temperature overnight

there was deposited of 200 mg of a solid. After two recrystallizations from methanol the collected L-tartrate salt was partitioned between dichloromethane and 10% sodium hydroxide solution, dried over sodium sulfate and evaporated to yield 116.6 mg of (-)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol with $[\alpha]_D$= -64.5° (c, 0.011 in $CHCl_3$) The other enantiomer (+)-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol $[\alpha]_D$= +64.5° (c, 0.011 in $CHCl_3$) was isolated from the mother liquor in the same manner.

The following known compounds can be prepared analogously or according to the methods known in the literature.

**1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 32): The procedure of example 6 is repeated, except that 1-ethyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (*J. Chem. Soc., Perkin Trans I* (1977) 2109-2115) is used instead of 1-isobutyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole.

**1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cβ-Dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene** (Compound 33) and **1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene** (Compound 34) and their **13b-epimers** (Compounds 35 and 36): The pure enamine from example 33 was reduced with sodium borohydride in methanol (containing a few drops of acetic acid) to give the two isomers, which are then separated by chromatography. The corresponding 13b-epimers are prepared by acid-catalysed epimerization of their parent isomers.

**2β-Methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-2-ol** (Compound 37) and **2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-2-ol** (Compound 38) are prepared following the procedures described in *J. Org. Chem.* **56** (1991) 2701-2712 and *Chem. Ber.* **106** (1973) 3106-3118. **1,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1α-ol** (Compound 39) and **1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1β-ol** (Compound 40) are prepared according to the procedure described in *Chem. Pharm. Bull.* **34** (1986) 3713-3721. **1,2,3,4,6,7,12,12b-Octahydro-indolo[2,3-*a*]quinolizine** (Compound 41) is prepared according to the method described in *J. C. S. Chem. Comm.*, (1972)

461. **1,4,6,7,12,12b-Hexahydro-indolo[2,3-*a*]quinolizine** (Compound 42) is prepared according to the method described in *Tetrahedron* **45** (1989) 3975-3992. **3,4,6,7,12,12b-Hexahydro-indolo[2,3-*a*]quinolizine** (Compound 43) and **1-ethyl-3,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** (Compound 44) are prepared according to the method described in *Bull. Soc. Chim. Fr.* **7-8** (1976) 1222. **1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 45) and **1β-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 46) are prepared according to the method described in *Tetrahedron* **45** (1989) 7615-7630. **1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 47) and **(1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 48) are prepared according to the method described in *Gazz. Chim. Ital.* **111** (1981) 257-267. **(1β-Ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 49) is prepared according to the method described in *Indian J. Chem., Sect. B* **22** (1983) 531. **3-Ethyl-2-methyl-1,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** (Compound 50) and **3α-ethyl-2α-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine** (Compound 51) are prepared according to the method described in *Tetrahedron* **46** (1990) 2633-2650. **2,3,5,6,7,11,11b-Hexahydro-1H-indolizino[8,7-*b*]indole** (Compound 52) is prepared according to the method described in *J. Org. Chem.* **53** (1988) 4236. **(1β,2,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol** (Compound 53) is prepared by reduction of the corresponding ester which synthesis is described in *Tetrahedron* **52** (1996) 9925. **1-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanol** (Compound 54) is prepared by reduction of its corresponding ketone which synthesis is described in *Tetrahedron Lett.* **30** (1989) 719. **1β-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 55) is prepared according to the method described in *J. Org. Chem.* **34** (1969) 330. **1α-Ethyl-1β-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 56) is prepared according to the method described in *J. Chem. Rsearch (S)* (1995) 382. **2β-*Tert*-butyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine** (Compound 57) and **2β-tert-butyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine** (Compound 58) are prepared according to the method described in *Tetrahedron* **45**

(1989) 3975. **2-*Tert*-butyl-1,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** (Compound 59) and **2-tert-butyl-3,4,6,7,12,12b-hexahydro-indolo[2,3-*a*]quinolizine** (Compound 60) are prepared according to the method described in *Tetrahedron* 47 (1991) 2879-2894. **(-)-1α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 61) and **(+)-1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol** (Compound 62) are obtained by resolution of their racemic mixture (Compound 47).

As already mentioned hereinbefore, the compounds of the present invention show interesting pharmacological properties, namely they exhibit affinity for alpha2 adrenoceptors. The said pharmacological activity of the compounds of the invention is demostrated with the pharmacological tests presented below.

EXPERIMENT I: **Radioligand binding to alpha2-adrenoceptors**

Examples of the alpha2-adrenoceptor binding affinities of the compounds including in the present invention are shown in the Table 1. Many of these compounds are high-affinity ligands for all the alpha2-receptors, but some of them display selectivity for the alpha2C-subtype.

Table 1. Calculated Ki values from radioligand binding assays using cells expressing human alpha2-adrenoceptor subtypes

| Compound | Binding affinity (Ki; nM) | | |
|---|---|---|---|
| | alpha2A | alpha2B | alpha2C |
| 4 | 480 | 330 | 61 |
| 5 | 130 | 160 | 25 |
| 7 | 710 | 580 | 87 |
| 14 | 29 | 81 | 17 |
| 20 | 30 | 110 | 26 |
| 32 | 280 | 45 | 23 |
| 42 | 150 | 460 | 85 |
| 46 | 210 | 520 | 75 |
| 47 | 359 | 245 | 31 |
| 48 | 85 | 20 | 18 |
| 49 | 440 | 470 | 110 |
| 50 | 130 | 1110 | 46 |
| 53 | 380 | 270 | 110 |
| 54 | 290 | 410 | 90 |
| 58 | 27 | 40 | 6,4 |

## EXPERIMENT II: *In vitro* antagonism on the alpha2-adrenoceptors

The functional activities of two compounds (47 and 48) displaying alpha2C-selectivity in binding experiments were determined as the abilities of the compounds to inhibit the epinephrine-stimulated binding of $^{35}$S-GTPγS to G proteins (Jasper, J.R. et al., *Biochem. Pharmacol.* **55(7)** (1998) 1035-44) in membranes of CHO cells stably transfected with the human alpha2-adrenoceptor subtypes. The antagonist potencies of compound 47 and compound 48 are presented in the Table 2. The results show that these compounds are selective antagonists for the alpha2C-subtypes.

Table 2. The mean antagonist potencies ($K_B$) of compound 47 and compound 48 on the human alpha2-adrenoceptor subtypes.

| Compound | Antagonist potency ($K_B$; nM) | | |
|---|---|---|---|
| | alpha2A | alpha2B | alpha2C |
| 47 | 295 | 351 | 23 |
| 48 | 320 | 75 | 4,2 |

### *In vivo* effects of alpha2C-selective compounds

It is currently not well-known in the art what effects *in vivo* could be attributed to a selective alpha2C-antagonism. Based on available knowledge and our previous experience, we have selected two different behavioral models, namely *d*-amphetamine –stimulated locomotor activity model and the forced swimming test, in order to demonstrate specific alpha2C-antagonistic effects in the CNS of mice and rats *in vivo*. The selection of these methods is essentially based on published hypotheses on theoretical effects of alpha2C-antagonists; in the lack of suitable ligands, these hypotheses were based on studies employing mice with genetically altered alpha2C-adrenoceptor expression (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85).

EXPERIMENT III: **D-amphetamine stimulated locomotor activity test**

Genetically modified mice having non-functional alpha2C-adrenoceptors (alpha2C-"knockout"; alpha 2C-KO) are more sensitive to the locomotor-enhancing effects of the psychostimulant d-amphetamine and, on the other-hand, over-expression of the alpha2C-adrenoceptor in mice (alpha2C-OE) leads to an opposite effect, i.e. to attenuation of the stimulant effect (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). Thus, it could be hypothesized that alpha2C-antagonist would potentiate the locomotor effects of d-amphetamine.

The above assumption was tested by administering groups of mice ($n$ = 10-12/dose group) amphetamine (4 micromol/kg s.c.) either alone or together with the alpha2C-antagonists (3 micromol/kg s.c.) of this invention or with the alpha2-subtype non-selective potent alpha2-antagonist (1 micromol/kg s.c.) (Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582), and by subsequently measuring the locomotor activity of mice with an automated infrared photobeam system designed for activity studies (PAS CageRack, SanDiego Instruments, San Diego, CA., USA). As expected, both of the tested alpha2C-selective antagonists increased the activity of mice (Figure 1a+b), as was expected for alpha2C-antagonist. The subtype non-selective alpha2-antagonist also potentiated the d-amphetamine effect. The tested compounds did not affect the baseline locomotor activity of mice (at doses between 0.1 – 10 mg/kg s.c.).

EXPERIMENT IV: **Antagonism of alpha2-agonist –induced sedation**

One of the prominent effects of non-selective alpha2-agonists in rodents is their ability to cause profound sedation. This effect, measured as locomotor inhibition by the alpha2-agonist dexmedetomidine was not modified in mice with genetically altered alpha2C-expression (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). On the other hand, alpha2-agonist did not have sedative effect in mice with genetically disrupted alpha2A-adrenoceptor (Hunter, J.C. et al., *British Journal of Pharmacology* **122(7)** (1997) 1339-44). Therefore, since the sedative effect of alpha2-agonists is generally attributed to the alpha2A-adrenoceptor, it is expected that alpha2C-antagonists would not modulate significantly the alpha2-agonist-induced sedation. This assumption was tested in experiment, where

dexmedetomidine was administered to mice pre-treated with the alpha2C-antagonists compound 47 or compound 48, or the subtype non-selective antagonist atipamezole (Haapalinna, A. et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* **356** (1997) 570-582). As expected, the alpha2C-antagonists did not have clear effects, whereas atipamezole effectively antagonised the effect of dexmedetomidine. This result demonstrates the lack of alpha2A-antagonism of the alpha2C-selective compounds of the present invention (Figure 2).

EXPERIMENT V: **Forced swimming test**

Forced swimming test (FST, i.e. Porsolt's test) is generally used in the pharmacological screening of new antidepressants. In this test, antidepressants increase the animals' activity compared to non-treated controls. Alpha2C-KO mice appeared to be more active, and alpha2C-OE mice were less active in FST (U.S. Patent No. 5,902,807 and Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). Therefore, it was tested, whether a selective alfa2C-antagonist would have antidepressant-like activity (e.g. activity-increasing property) in the FST. The figure 3 shows how both of the alpha2C-compounds increased activity in this test as was expected based on studies on transgenic mice (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85) and as reported with recently developed alpha2C-antagonist (WO 01/64645). Also the positive control substances desipramine and fluoxetine (clinically effective antidepressant agents) were active. The subtype non-selective alpha2-antagonist atipamezole did not possess antidepressant-like effect, as expected (WO 01/64645).

EXPERIMENT VI: **Prepulse inhibition of the startle reflex**

Prepulse-inhibition (PPI) of a startle response refers to the reduction in the startle response caused by a low intensity non-startling stimulus (the prepulse) which is presented shortly before the startle stimulus. PPI can be used as an operational measure of sensorimotor gating and appears to be present in all mammals, including rats and humans (Swerdlow, N.R. et al., *The archives of general psychiatry* **51** (1994) 139-154). Normally functioning PPI can be disrupted by psychostimulants, such as d-amphetamine or phencyclidine (PCP), and reversed by clinically effective antipsychotics.

In a previous study, alpha2C-KO mutation was associated with weakened PPI whereas alpha2C-OE demonstrated increased PPI. In other words, the genetically altered alpha2C-expression in mice was associated with changes in PPI in a way suggesting that an alpha2C-antagonist would decrease PPI (Scheinin, M. et al., *Life Sci* **68(19-20)** (2001) 2277-85). This hypothesis was tested with compounds 47 and 48 alone and against PCP –disruption of the PPI.

Groups of rats (n =10/group) were administered the alpha2C-antagonists 20 min before, and PCP or vehicle 10 min before measurement of the acoustic startle reactivity and PPI in a test system designed for startle studies (SR-LAB, San Diego Instruments, CA, USA). It was found that the alpha2C-antagonists were able to attenuate the PPI disruption caused by PCP (Figure 3). This was unexpected and opposite to the hypothesis based on transgenic studies. The non-selective alpha2-antagonist atipamezole produced different effects than was observed with the selective alpha2C-antagonists: atipamezole did not enhance PPI, but it increased the startle reflex per se (i.e. startle without prepulses)(Figure 4).

In conclusion, the results presented in this chapter show that those antagonists which are classified as alpha2C-selective according to *in vitro* experiments, appeared to function as alpha2C-selective antagonists also *in vivo* in a manner that was predicted based on the available knowledge on alpha2C-antagonism. However, the finding that the alpha2C-antagonists did not decrease PPI, as predicted, but on the contrary, increased PPI, could be considered unexpected and this adds the novelty value of the now proposed usefulness of the compounds of the present invention.

The compounds according to the invention may be used to treat any disease or condition wherein alpha-2 antagonists are indicated to be effective. The compounds can also be used to reverse effects induced by alpha-2 agonists. Accordingly, the compounds of the invention may be useful in the treatment of various disorders of the central nervous system (CNS), i.e. different neurological, psychiatric and cognition disorders (such as depression, anxiety disorders, post traumatic stress disorder, schizophrenia, Parkinson's disease and other movement disorders). Furthermore, they may be used in the treatment of various peripheral disorders, e.g.

diabetes, orthostatic hypotension, lipolytic disorders (such as obesity) or both male and female sexual dysfunctions.

The selective alpha-2C antagonists of the present invention may be used for the treatment of various disorders or conditions of CNS-system where alpha-2C antagonists are indicated to be beneficial, for example, to alleviate the symptoms of various mental disorders propagated by stress, Parkinson's disease, depression, negative symptoms of schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress-disorder, or anxiety disorders.

In addition, due to the novel and previously unpublished findings of the effects of the present alpha2C-antagonists on the PCP –disrupted PPI, the alpha2C-selective compounds can also be used to treat disorders and conditions associated with sensorimotor gating deficits, particularly disorders and conditions wherein the sensorimotor gating deficits results in sensory flooding and cognitive fragmentation causing dysfunction in attention and perception. Such disorders and conditions include, but are not limited to, schizophrenia, obsessive compulsive disorder, Tourette's syndrome, blepharospasm and other focal dystonias, temporal lobe epilepsy with psychosis, drug-induced psychosis (for example, psychosis caused by chronic use of dopaminergic agents) (Braff, D.L. et al., *Psychopharmacology (Berl)* **156(2-3)** (2001) 234-258), Huntington's disease, Parkinson's disease, disorders caused by fluctuation of the levels of sex hormones (such as premenstrual syndrome), and panic disorder.

Further, the symptoms which are usually associated with above-mentioned disorders or conditions include, but are not limited to, hallucination, delusion, parathymia, agitation, psychotic cognitive impairment (including deficits in thinking and speech), social withdrawal and withdrawal symptoms (including delirium) associated with cessation of cigarette smoking or alcohol or drug abuse. These symptoms may also be seen in animals in exceptional circumstances, for example, during withdrawal from masters or during transportation.

Due to their selectivity of action, the alpha-2C antagonists of the invention have less or no undesirable side-effects attributed to non-selective alpha2-antagonism, such as increases in blood pressure, heart rate, salival secretions,

gastrointestinal secretion, anxiety, and startle reactivity per se (Ruffolo, R.R.J. et al., *Annu Rev Pharmacol Toxicol* **32** (1993) 243-279).

The compound of the invention can be administered for example enterally, topically or parenterally by means of any pharmaceutical formulation useful for said administration, and containing at least one active compound of formula I in pharmaceutically acceptable and effective amounts together with pharmaceutically acceptable diluents, carriers, and/or excipients known in the art. The manufacture of such pharmaceutical formulations is well known in the art.

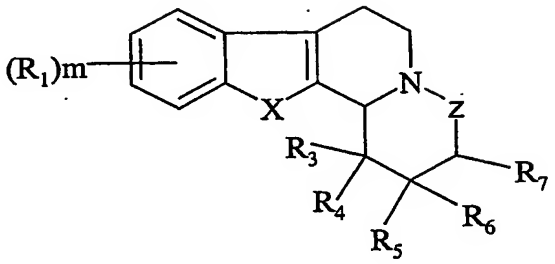
The therapeutic dose to be given to a patient in need of treatment will vary depending on the compound being administered, the species, age and the sex of the subject being treated, the particular condition being treated, as well as the route and method of administration, and are easily determined by person skilled in the art. Accordingly, the typical dosage for oral administration is from 5 μg/kg to 100 mg/kg per day and that for parenteral administration from 0.5 μg/kg to 10 mg/kg for an adult mammal.

The present invention further provides a compound of the invention or an ester or salt thereof for use as alpha-2 antagonist. Furthermore, a method for the treatment of diseases or conditions where alpha-2 antagonists, e.g. alpha-2C antagonists, are indicated to be useful, e.g. a method for the treatment of diseases or conditions of the central nervous system, is provided. In such a method a therapeutically effective amount of a compound of the invention is administered to a subject in need of such treatment. The use of the compounds of the invention for the manufacture of a medicament to be used for the above indications is also provided.

Those skilled in the art will appreciate that the embodiments described in this application could be modified without departing from the broad inventive concept. Those skilled in the art also understand that the invention is not limited to the particular disclosed embodiments, but is intended to also cover modifications to the embodiments that are within the spirit and scope of the invention.

## CLAIMS

1. Use of a compound of formula I,



I

wherein,

X is $CH_2$, O, S or $NR_2$;

Z is $-CHR_8-(CH_2)n-$ or a single bond;

$R_1$ is hydroxy, $(C_1-C_6)$alkyl, $OCH_3$, halogen or halo$(C_1-C_6)$alkyl;

$R_2$ is H or $(C_1-C_6)$alkyl

$R_3$ is H, hydroxy, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, $(C_3-C_7)$cycloalkyl, hydroxy$(C_1-C_6)$alkyl, halo$(C_1-C_6)$alkyl, amino$(C_1-C_6)$alkyl or one of $R_3$ or $R_4$ and $R_6$ together form a bond between the ring atoms to which they are attached;

$R_4$ is H, hydroxy, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy or hydroxy$(C_1-C_6)$alkyl;

$R_5$ is H, hydroxy, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy or hydroxy$(C_1-C_6)$alkyl or $R_4$ and $R_5$ form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring optionally substituted with 1 to 3 substituent(s) $R_9$ each independently being hydroxy, $(C_1-C_6)$alkyl, halogen, amino, nitro, $(C_3-C_7)$cycloalkyl, hydroxy$(C_1-C_6)$alkyl, halo$(C_1-C_6)$alkyl, amino$(C_1-C_6)$alkyl, mono- or di$(C_1-C_6)$alkylamino, mono- or di$(C_1-C_6)$alkylamino$(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, carboxyl, $(C_1-C_6)$alkyl-CO-, $(C_1-C_6)$alkoxy-CO-, $(C_1-C_6)$alkoxy-CO-$(C_1-C_6)$alkyl or $NH_2$-CO-;

$R_6$ is H, hydroxy, $(C_1-C_6)$alkyl, hydroxy$(C_1-C_6)$alkyl or $R_6$ forms a bond between the ring atom to which it is attached and the ring atom to which $R_7$ is attached;

$R_7$ is H, $(C_1-C_6)$alkyl or hydroxy$(C_1-C_6)$alkyl;

$R_8$ is H or ($C_1$-$C_6$)alkyl or, only when n is 0, $R_7$ and $R_8$ form, together with the carbon ring atoms to which they are attached, a condensed five to seven membered saturated carbocyclic ring optionally substituted with 1 to 3 substituent(s) $R_{10}$ each independently being hydroxy, ($C_1$-$C_6$)alkyl, halogen, amino, nitro, ($C_3$-$C_7$)cycloalkyl, hydroxy($C_1$-$C_6$)alkyl, halo($C_1$-$C_6$)alkyl, amino($C_1$-$C_6$)alkyl, mono- or di($C_1$-$C_6$)alkylamino, mono- or di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy, carboxyl, ($C_1$-$C_6$)alkyl-CO-, ($C_1$-$C_6$)alkoxy-CO-, ($C_1$-$C_6$)alkoxy-CO-($C_1$-$C_6$)alkyl or $NH_2$-CO-;

$R_7$ and $R_8$ are attached to the carbon ring atoms, which are adjacent;

m is 0 to 2; and

n is 0 or 1,

or of a pharmaceutically acceptable salt or ester thereof, with the proviso, that when X is O, n is 0, $R_1$, $R_3$, $R_4$, $R_7$ and $R_8$ are hydrogen, and one of $R_5$ or $R_6$ is hydrogen, then the other $R_5$ or $R_6$ is not hydroxy($C_1$-$C_6$)alkyl,

for the manufacture of a medicament for the treatment of diseases or conditions where antagonists of alpha-2 adrenoceptors are indicated to be useful.

2. The use of a compound of formula I according to claim 1, wherein X is $NR_2$.

3. The use of a compound of formula I according to any one of claims 1 or 2, wherein X is $NR_2$, $R_1$ is H, $R_3$ is ($C_1$-$C_6$)alkyl and $R_4$ is hydroxy or hydroxy($C_1$-$C_6$)alkyl.

4. The use of a compound of formula I according to any one of claims 1 to 3, wherein the compound is 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1β-ethyl-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol or 1,2,3,4,4aβ,5,6,7,8,13,13bβ,13cα-dodecahydro-6a,13-diaza-indeno-[1,2-*c*]phenanthrene.

5. The use of a compound of formula I according to claim 1, wherein X is $CH_2$, O or S.

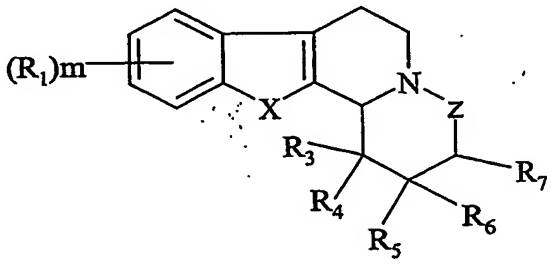
6. The use according to any one of claims 1 to 5, for the manufacture of a medicament for the treatment of a disorder of the central nervous system, diabetes, orthostatic hypotension, lipolytic disorders, or male and female sexual dysfunctions.

7. The use according to claim 6, wherein the disorder of the central nervous system is depression, anxiety disorders, post-traumatic stress disorder, schizophrenia, Parkinson's disease, or another movement disorder.

8. The use of a compound of formula I according to any one of claims 1 to 5 for the manufacture of a medicament for use as a selective alpha-2C antagonist.

9. The use according to claim 8 for the manufacture of a medicament for the treatment of mental disorders propagated by stress, Parkinson's disease, depression, negative symptoms of schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress-disorder, or anxiety disorders.

10. A compound of formula IA




IA

wherein,

X is $CH_2$, O or S;

Z, $R_1$, $R_3$-$R_{10}$, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt or ester thereof, with the provisos, that

a) when X is S and Z is a single bond or n is 0, then $R_1$ and $R_3$-$R_8$ are not all simultaneously hydrogen;

b) when X is O and n is 0, then $R_1$ and $R_3$-$R_8$ are not all simultaneously hydrogen;

c) when X is O, n is 0, $R_1$, $R_3$, $R_4$, $R_7$ and $R_8$ are hydrogen, and one of $R_5$ or $R_6$ is hydrogen, then the other $R_5$ or $R_6$ is not hydroxy($C_1$-$C_6$)alkyl.

11. A compound according to claim 10, wherein X is $CH_2$.

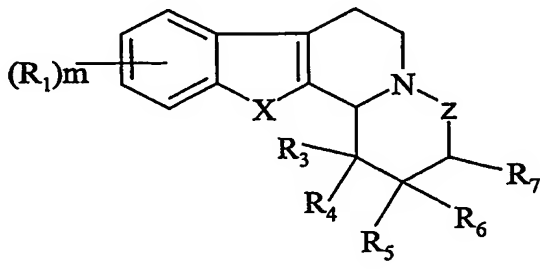
12. A compound according to claim 10, wherein X is O.

13. A compound according to claim 10, wherein X is S.

14. A compound according to any one of claims 10 to 13, wherein $R_3$ is ($C_1$-$C_6$)alkyl, $R_4$ is hydroxy or hydroxy($C_1$-$C_6$)alkyl.

15. A compound according to claim 10, wherein the compound is 1α-Methyl-1,3,4,5,6,11b-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, (1α-Methyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol, 1α-Isopropyl-1,3,4,5,6,11b-Hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol, 1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-ol or (1α-Ethyl-1,3,4,5,6,11bβ-hexahydro-2H-11-oxa-4a-aza-benzo[a]fluoren-1-yl)-methanol.

16. A compound of formula IB




IB

wherein,

X is $NR_2$;

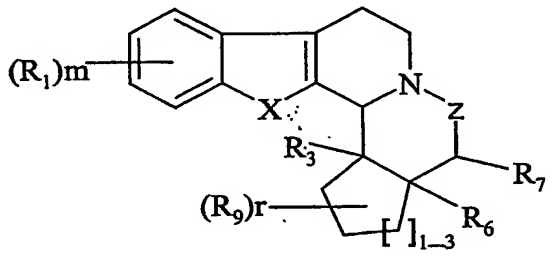
$R_2$ is $(C_1\text{-}C_6)$alkyl;

Z, $R_1$, $R_3$-$R_{10}$, m and n are as defined in claim 1,

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 2,3-Diethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizine; 12-Methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-ol; 2-(1-Ethyl-12-methyl-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-ethanol; 11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indole; (11-Methyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol or (1,11-Diethyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-*b*]indol-1-yl)-methanol.

17. A compound according to claim 16, wherein the compound is 1α-Ethyl-12-methyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol or 1α-Ethyl-12-ethyl-1,2,3,4,6,7,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol.

18. A compound of formula IC




IC

wherein,

X is $NR_2$;

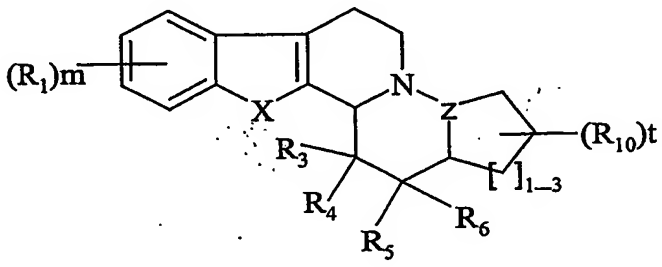
Z, $R_1$, $R_2$, $R_3$, $R_6$, $R_7$, $R_8$, $R_9$, m and n are as defined in claim 1;

r is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,7,8,13,13b,13c-Dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 13-Methyl-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-*c*]phenanthrene; 5,7,7a,8,9,10,11,11a,11b,12-Decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 10-Methyl-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-Methoxy-5,7,7a,8,9,10,11,11a,11b,12-decahydro-6H-6a,12-diaza-indeno[1,2-*a*]fluorene; 3-Hydroxy-1,2,3,4,4a,5,6,7,8,13,13b,13c-dodecahydro-6a,13-diaza-indeno[1,2-c]phenanthrene-4-carboxylic acid methyl ester; Methyl-3-ethyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopen[a]idolizine-2-carboxylate or Methyl-1,2,3a,4,6,7,12b,12c-octahydro-3H,12H-indolo[2,3-*g*]cyclopen[a]idolizine-2-carboxylate.

19. A compound according to claim 18, wherein the compound is 2,3,4,4aβ,5,6,7,8,13,13bβ-decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthren-13cβ-ol, (2,3,4,4aβ,5,6,7,8,13,13bβ-Decahydro-1H-6a,13-diaza-indeno[1,2-*c*]phenanthrenyl)-13cβ-methanol or 5,6,7,7a,11,11b,12-Decahydro-6a,12-diaza-indeno[1,2-*a*]fluoren-11a-ol.

20. A compound of formula ID




ID

wherein,

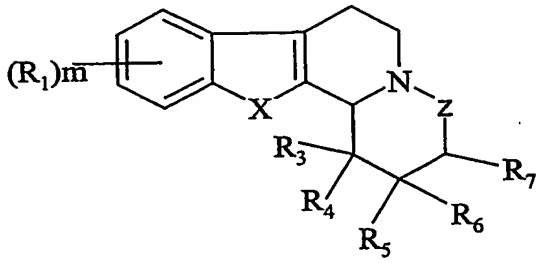
X is $NR_2$;

Z, $R_1$-$R_{10}$, m and n are as defined in claim 1;

t is 0 to 3;

or a pharmaceutically acceptable salt and ester thereof, with the provisos, that the compound is not 1,2,3,4,4a,5,6,11,11b,12,13,13a-Dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 1,2,3,4,4a,5,6,11,11b,12-Decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene; 9-Methoxy-1,2,3,4,4a,5,6,11,11b,12-decahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene or 1-Hydroxy-1,2,3,4,4a,5,6,11,11b,12,13,13a-dodecahydro-4b,11-diaza-indeno[2,1-*a*]phenanthrene-2-carboxylicacid methyl ester.

21. A compound of formula IE



IE

wherein,

X, Z, $R_1$-$R_{10}$ and m are as defined in claim 1;

n is 1,

or a pharmaceutically acceptable salt and ester thereof, with the proviso, that the compound is not 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido-[3,4-b]indole-2-ethyl-2-methanol; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2-methanol,4-ethyl; 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole-2,3-diethyl or 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido-[3,4-*b*]indole-2-methanol.

22. A compound according to claim 21, wherein the compound is 2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1',2':1,2]pyrido[3,4-*b*]indole.

23. A compound which is 2β-Methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 2α-methoxy-1,2,3,4,6,7,12,12bα-octahydro-indolo[2,3-*a*]quinolizine, 1α-Ethyl-2α-methyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, 1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-

*a*]quinolizin-1-ol, 1β-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizine, (1α-Isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α- *n*-Propyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-yl)-methanol, 2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-butan-2-ol, 1-(1,2α,3,4,6,7,12,12bα-Octahydro-indolo[2,3-*a*]quinolizin-2-yl)-propan-1-ol, 2-(1α,2,3,4,6,7,12,12bβ-Octahydro-indolo[2,3-*a*]quinolizin-1-yl)-propan-2-ol, 1-*s*-Butyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 1-Cyclohexyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-ol, 9-Fluoro-1α-isopropyl-1,2,3,4,6,7,12,12bβ-octahydro-indolo[2,3-*a*]quinolizin-1-ol, (1α-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, (1α-Ethyl-1,4,6,7,12,12bβ-hexahydroindolo[2,3-*a*]quinolizin-1-yl)-methanol, 3β,4α-Dimethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine, (1,2α,3,4,6,7,12,12bα-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (1,2α,3,4,6,7,12,12bβ-Octahydroindolo[2,3-*a*]quinolizin-2-yl)-propan-2-ol, (2α-Ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol or (2α-Ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-2-yl)-methanol.

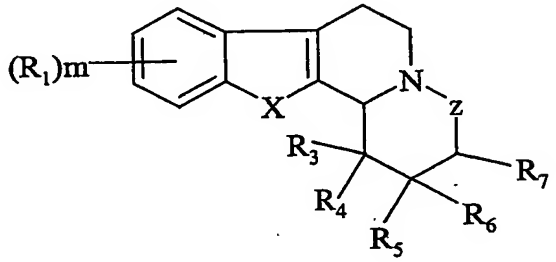
24. A pharmaceutical composition comprising at least one compound according to any one of claims 10 to 23 and a pharmaceutically acceptable diluent, carrier and/or excipient.

25. A compound according to any one of claims 10 to 24 for use as a medicament.

26. A method for the treatment of a disease or condition where an antagonist of alpha-2 adrenoceptors is indicated to be useful, which comprises administering to a mammal in need of the treatment an effective amount of at least one compound of formula I according to claim 1.

## ABSTRACT

The invention provides a compound of formula I,



I

wherein X, Z, $R_1$ to $R_{10}$, m, n, r and t are as defined in claim 1, or a pharmaceutically acceptable salt or ester thereof, useful as an alpha-2 antagonist. The compounds of formula I can be used for the treatment of diseases or conditions where antagonists of alpha-2 adrenoceptors are indicated to be effective.

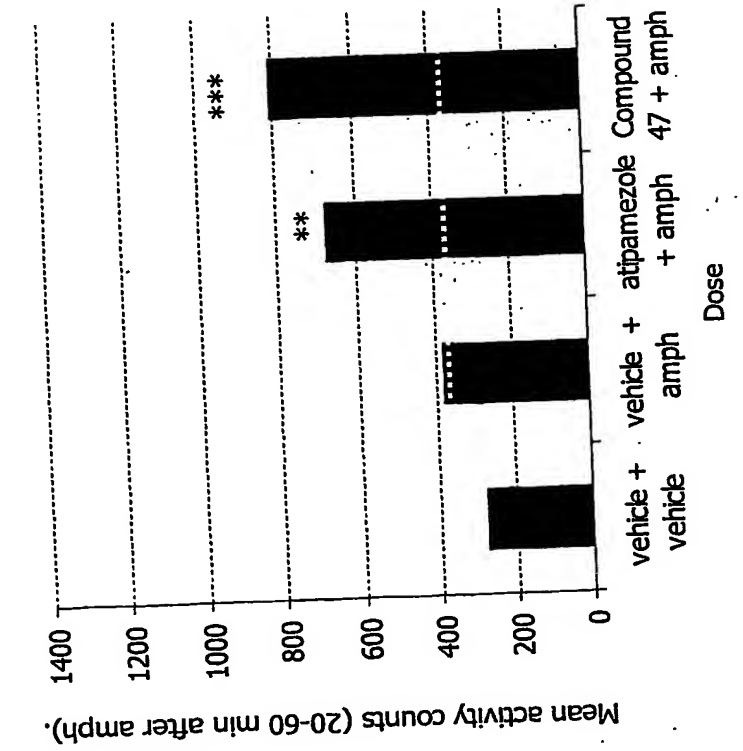

Mean activity counts (20-60 min after amph).
1400
1200
1000
800
600
400
200
0
***
**
vehicle + vehicle
vehicle + amph
atipamezole + amph
Compound 47 + amph
Dose

FIG. 1a

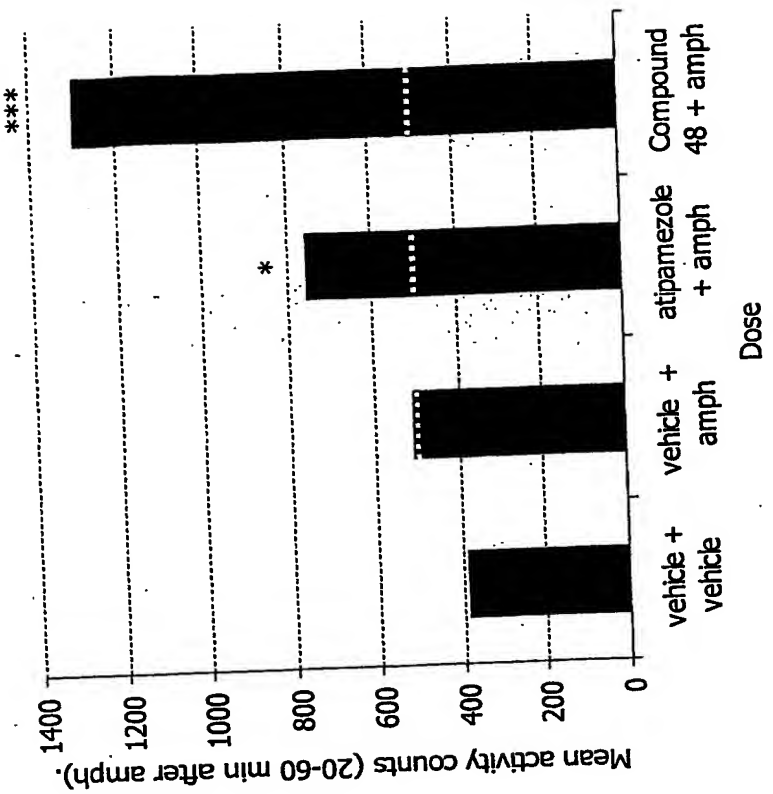

Mean activity counts (20-60 min after amph).
1400
1200
1000
800
600
400
200
0
***
*
vehicle + vehicle
vehicle + amph
atipamezole + amph
Compound 48 + amph
Dose

FIG. 1b

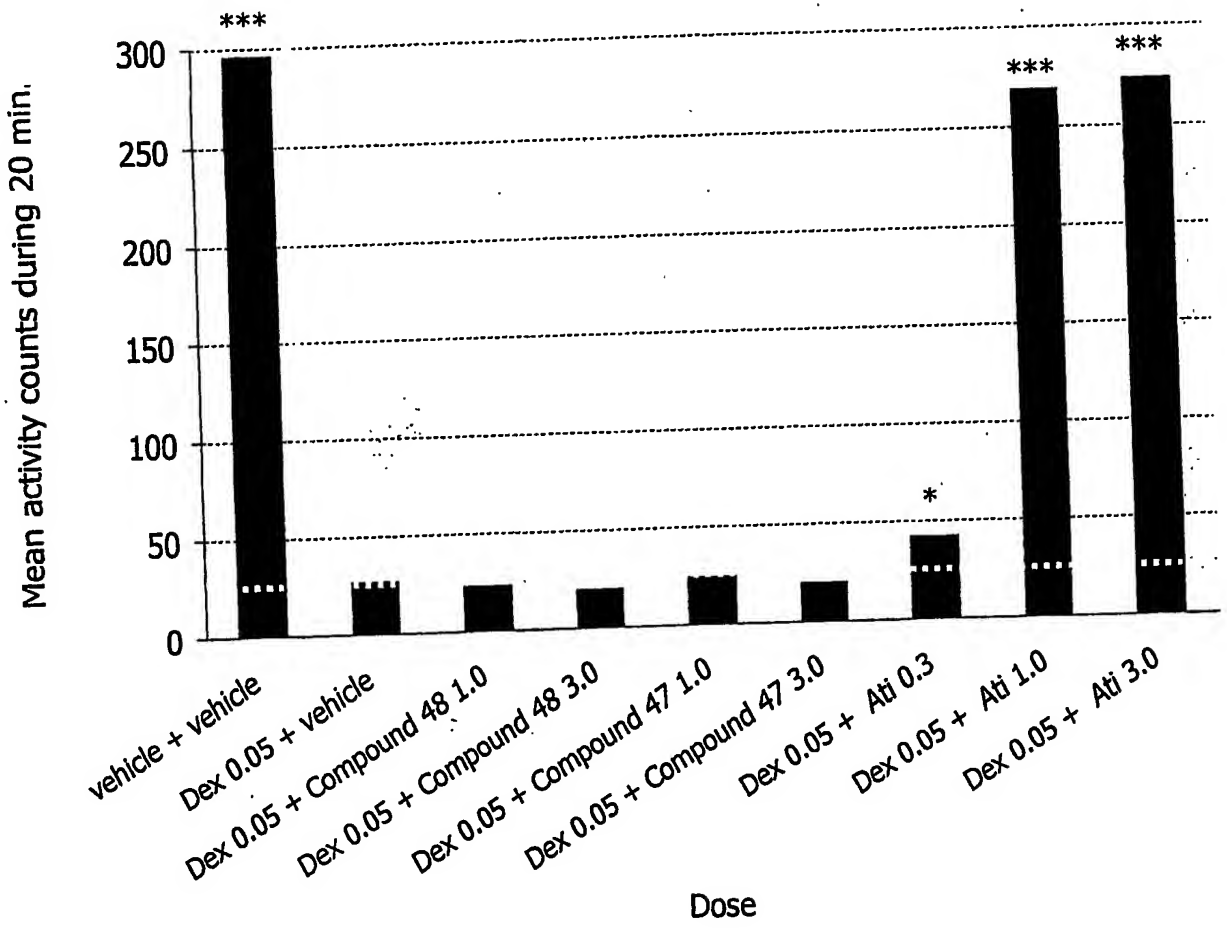

***
***
***
*
300
250
200
150
100
50
0
Mean activity counts during 20 min.
vehicle + vehicle
Dex 0.05 + vehicle
Dex 0.05 + Compound 48 1.0
Dex 0.05 + Compound 48 3.0
Dex 0.05 + Compound 47 1.0
Dex 0.05 + Compound 47 3.0
Dex 0.05 + Ati 0.3
Dex 0.05 + Ati 1.0
Dex 0.05 + Ati 3.0
Dose

FIG. 2

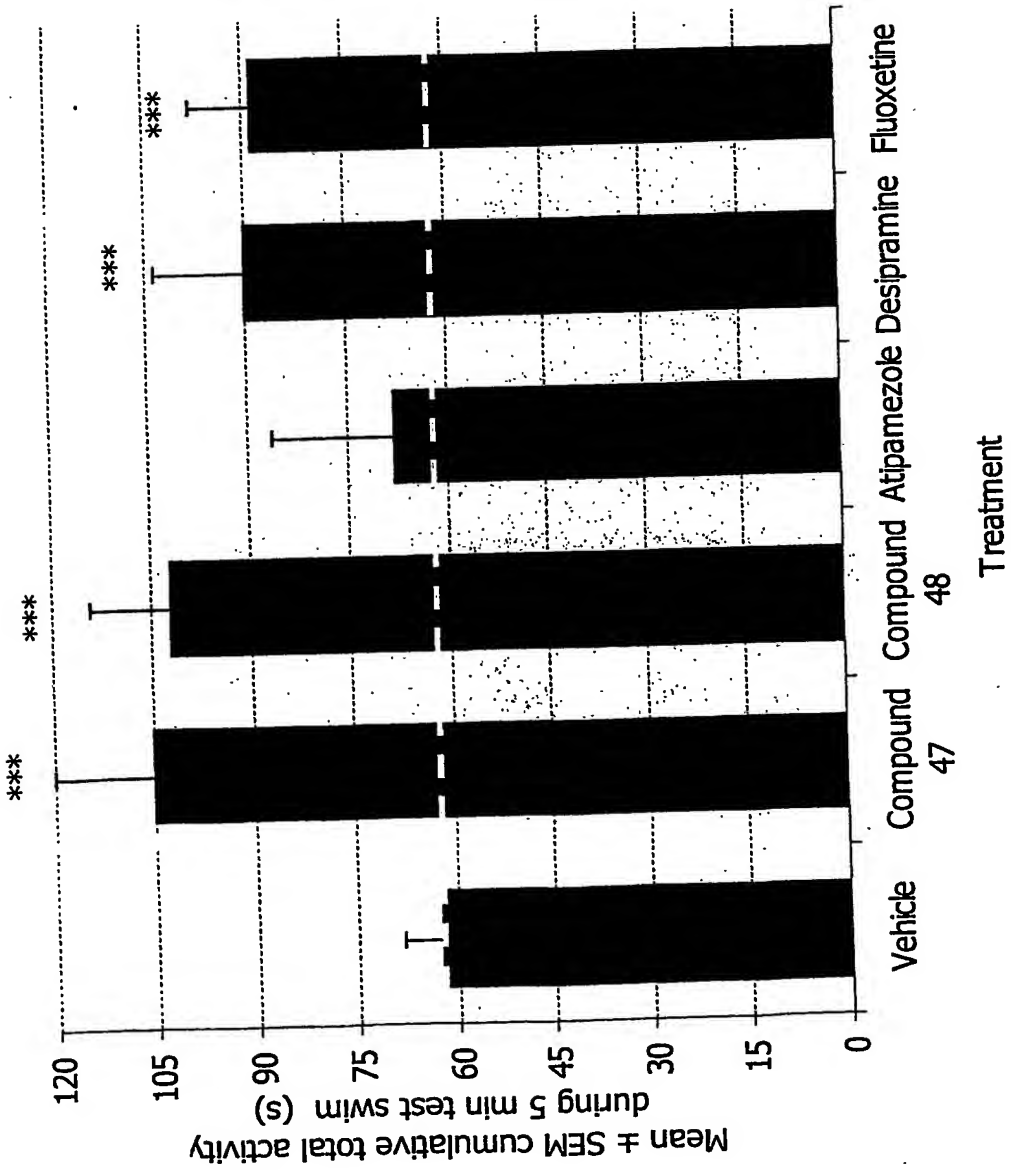

Mean ± SEM cumulative total activity
during 5 min test swim (s)
120
105
90
75
60
45
30
15
0
***
***
***
Vehicle
Compound 47
Compound 48
Atipamezole
Desipramine
Fluoxetine
Treatment

FIG 3.

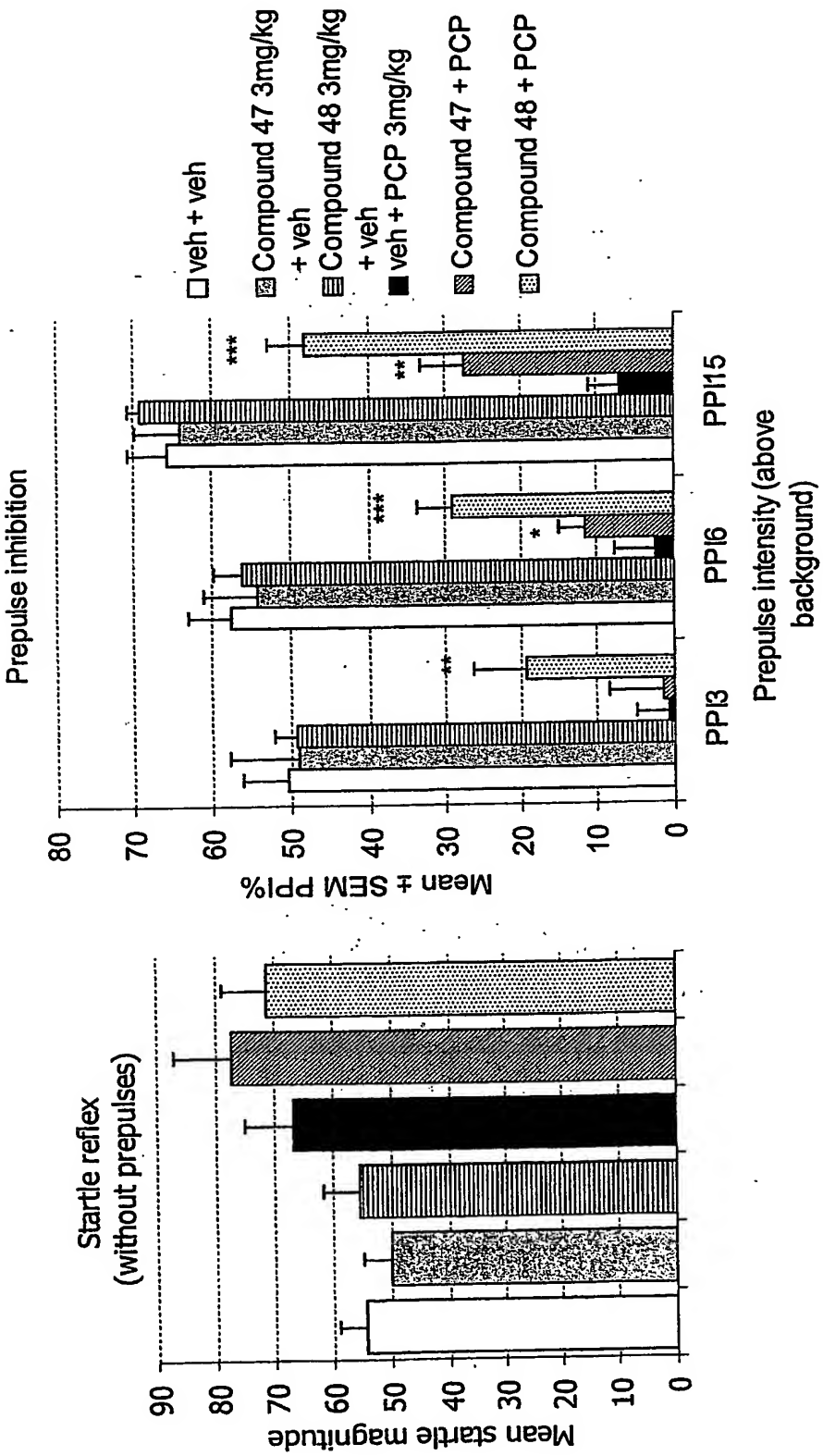

Prepulse inhibition
Mean ± SEM PPI%
Prepulse intensity (above background)
PP3
PP6
PPI5
veh + veh
Compound 47 3mg/kg + veh
Compound 48 3mg/kg + veh
veh + PCP 3mg/kg
Compound 47 + PCP
Compound 48 + PCP
Startle reflex (without prepulses)
Mean startle magnitude

FIG. 4b

FIG. 4a

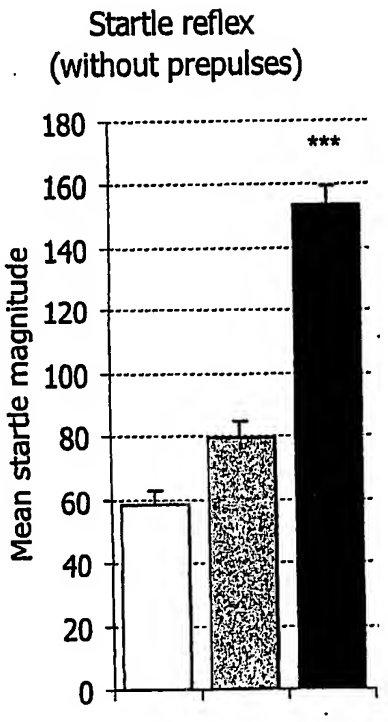

Startle reflex
(without prepulses)
Mean startle magnitude
180
160
140
120
100
80
60
40
20
0
***

FIG. 5a

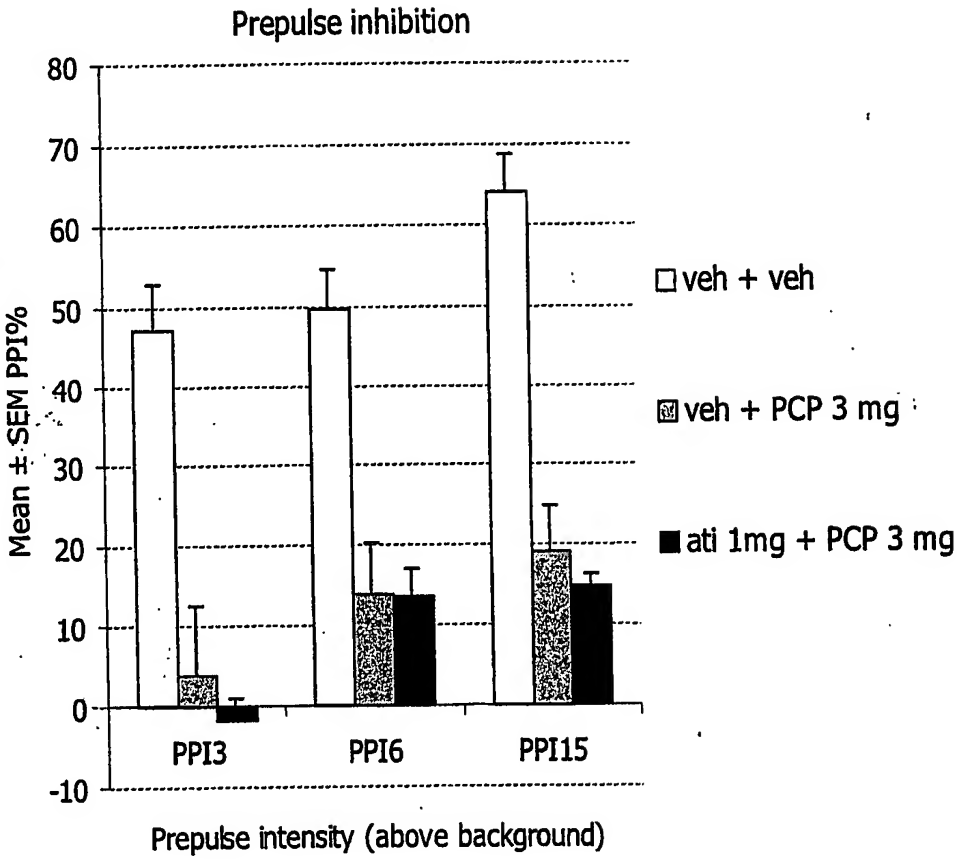

Prepulse inhibition
Mean ± SEM PPI%
80
70
60
50
40
30
20
10
0
-10
PPI3
PPI6
PPI15
Prepulse intensity (above background)
veh + veh
veh + PCP 3 mg
ati 1mg + PCP 3 mg

FIG.5b